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1,5-Benzoxathiepin Derivatives. II.[1] Synthesis and Serotonin S₂-Receptor-Blocking Activity of Aminoalkyl-Substituted 3,4-Dihydro-2H-1,5-benzoxathiepin-3-ols and Related Compounds

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Novel 1,5-benzoxathiepin derivatives, 3,4-dihydro-2H-1,5-benzoxathiepin-3-ols with an aminoalkyl group at the 2-, 3- or 4-position, were synthesized and evaluated for serotonin S₂-receptor-blocking activity and adrenergic α₁-receptor-blocking activity. Methyl 4-aminoalkyl-3-hydroxy-3,4-dihydro-2H-1,5-benzoxathiepin-4-carboxylates showed significant S₂-receptor-blocking activities. Structure–activity relationships (including the results of a conformational study and skeletal modifications) were examined. In the series of 1,5-benzoxathiepin, 1-benzoxepin and 1-benzothiepin derivatives, methyl cis-3-hydroxy-7-methoxy-4-[3-(4-phenyl-1-piperazinyl)propyl]-3,4-dihydro-2H-1,5-benzoxathiepin-4-carboxylate hydrochloride (CV-5197) showed the most potent and the most selective S₂-receptor-blocking activity in the binding profile, and was chosen as a candidate for further pharmacological evaluation.

Keywords——seven-membered heterocycle; 1,5-benzoxathiepin derivative; aminoalkyl-substituted 3,4-dihydro-2H-1,5-benzoxathiepin-3-ol; serotonin S₂-receptor antagonist; structure–activity relationship; 1,5-benzoxathiepin derivative conformation; CV-5197

Serotonin (5-hydroxytryptamine, 5-HT) is known to act as a chemical mediator in a wide variety of physiological actions. Peroutka and Snyder demonstrated the existence of distinct populations of serotonin receptors, S_1 or 5-HT₁ and S_2 or 5-HT₂ receptors, based on the binding characteristics of radio-labeled serotonin and spiperone in rat brain homogenate, respectively.[2] Peripheral vascular serotonergic receptors have the pharmacological characteristics of receptors such as S_2-receptors in the central nervous systems.[3] Ketanserin, which is a potent and selective S_2-receptor antagonist, is a member of a new class of drugs possessing effective antihypertensive activity.[4] However, recent studies suggest that the antihypertensive effect of ketanserin in animal models is more related to its postsynaptic adrenergic α₁-receptor-blocking activity than to its antagonism of vascular S_2-receptors, and the apparent role of serotonin in hypertension is still uncertain.[5] Nevertheless, platelet aggregation due to serotonin is mediated through S_2-receptors.[6] Furthermore, serotonin has an amplifying effect on vascular and platelet actions, which is also mediated through S_2-receptors.[4,6,7] Thus, the selective antagonism of S_2-receptors might be important in preventing peripheral circulatory disorders in which vasoconstriction and platelet aggregation are suggested to be involved. In a study of the structure–activity relationships of S_2-receptor antagonists, no distinct structural relationships among serotonin and antagonists were found except for the essential amino function in the molecules.[8] Diltiazem, classified as a Ca antagonist having a structure with the seven-membered 1,5-benzothiazepine skeleton, caused reduction of the serotonin-induced contraction in isolated rabbit basilar artery, whereas such a reduction was diminished in the aorta.[9]
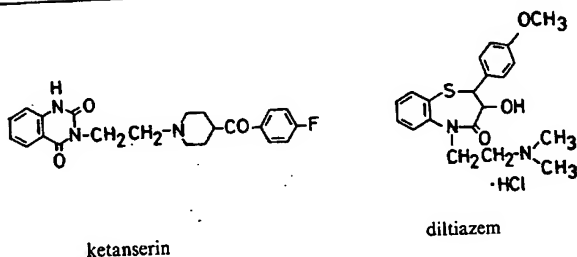
ketanserin

diltiazem

Chart 1

With the aim of finding a novel S_2-receptor blocker, we synthesized 1,5-benzoxathiepin derivatives having structures analogous to 1,5-benzothiazepines and found that the 3,4-dihydro-2H-1,5-benzoxathiepin-3-ols with an aminoalkyl group at the 4-position showed significant S_2-receptor-blocking activities. In this paper, we report the syntheses of the 1,5-benzoxathiepins with an aminoalkyl group at the 2-, 3-, or 4-position and related compounds, and the structure-activity relationships of S_2-receptor-blocking activity.

Synthesis of Aminoalkyl-Substituted 1,5-Benzoxathiepin Derivatives and Related Compounds

In the previous paper, we reported a novel synthetic route to the 1,5-benzoxathiepin skeleton and some modifications at its 2-, 3-, and 4-positions.[1] We first examined the introduction of an aminoalkyl group into the 4-position of methyl 3-oxo-3,4-dihydro-2H-1,5-

a series: $R_1 = H$,   b series: $R_1 = 7\text{-OCH}_3$,
c series: $R_1 = 8\text{-OCH}_3$,   d series: $R_1 = 7\text{-Cl}$,
e series: $R_1 = 7\text{-CH}_3$,   f series: $R_1 = 7\text{-OCH}_2\text{Ph}$,
g series: $R_1 = 7\text{-OH}$

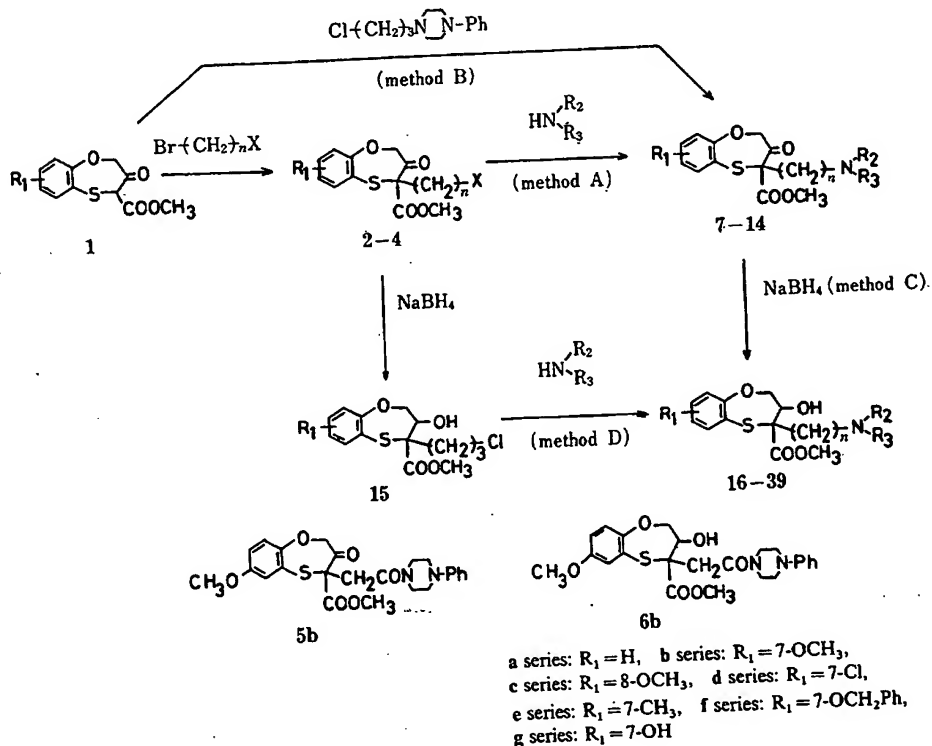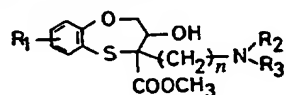Chart 2

Table 1. Physicochemical Properties of Methyl 4-Aminoalkyl-Substituted 3-Hydroxy-3,4-dihydro-2H-1,5-benzoxathiepin-4-carboxylates (16—39)

Compd. No.	R$_1$	N$\langle$R$_2$ / R$_3$	n	Meth-od[a]	Yield (%)	mp (°C)	Formula	C	H	N
cis-16b	7-OCH$_3$	N⬡N–Ph	2	F	42	213—216	C$_{24}$H$_{30}$N$_2$O$_5$S· 2HCl	54.24 (54.14	6.07 6.08	5.27 5.29)
cis-17a	H	N⬡N–Ph	3	C	52	196—198	C$_{24}$H$_{30}$N$_2$O$_4$S· 2HCl	55.92 (55.73	6.26 6.15	5.45 5.51)
trans-17a	H	N⬡N–Ph	3	C	38	165—170	C$_{24}$H$_{30}$N$_2$O$_4$S· 2HCl·1/4H$_2$O	55.43 (55.47	6.30 6.19	5.39 5.40)
cis-17b	7-OCH$_3$	N⬡N–Ph	3	C D	47 56	154—155	C$_{25}$H$_{32}$N$_2$O$_5$S· HCl·2H$_2$O	55.09 (55.46	6.84 6.77	5.14 5.09)
trans-17b	7-OCH$_3$	N⬡N–Ph	3	C	31	140—145	C$_{25}$H$_{32}$N$_2$O$_5$S· HCl·H$_2$O	56.97 (56.67	6.69 6.70	5.31 5.35)
cis-17c	8-OCH$_3$	N⬡N–Ph	3	C	46	195—198	C$_{25}$H$_{32}$N$_2$O$_5$S· HCl·1/4H$_2$O	58.47 (58.43	6.57 6.44	5.46 5.62)
trans-17c	8-OCH$_3$	N⬡N–Ph	3	C	30	170—175	C$_{25}$H$_{32}$N$_2$O$_5$S· 2HCl·1/2H$_2$O	54.12 (54.08	6.36 6.02	5.05 5.03)
cis-17d	7-Cl	N⬡N–Ph	3	C	42	205—207	C$_{24}$H$_{29}$ClN$_2$O$_4$S· 2HCl·1/2H$_2$O	51.57 (51.77	5.77 5.79	5.01 4.97)
trans-17d	7-Cl	N⬡N–Ph	3	C	38	150—160	C$_{24}$H$_{29}$ClN$_2$O$_4$S· 2HCl	52.42 (52.24	5.68 5.76	5.09 4.97)
cis-17e	7-CH$_3$	N⬡N–Ph	3	C	48	170—175	C$_{25}$H$_{32}$N$_2$O$_4$S· 2HCl	56.70 (56.73	6.47 6.54	5.01 5.04)
trans-17e	7-CH$_3$	N⬡N–Ph	3	C	33	145—155	C$_{25}$H$_{32}$N$_2$O$_4$S· 2HCl·1/4H$_2$O	56.23 (56.39	6.51 6.53	5.25 5.24)
cis-17f	7-OCH$_2$Ph	N⬡N–Ph	3	D	61	198—201	C$_{31}$H$_{38}$N$_2$O$_5$S· HCl	63.62 (63.32	6.37 6.41	4.79 4.52)
cis-17g	7-OH	N⬡N–Ph	3	E	64	207—209	C$_{24}$H$_{30}$N$_2$O$_5$S	62.86 (62.61	6.59 6.50	6.11 5.88)
cis-18b	7-OCH$_3$	N⬡N–Ph	4	C	75	168—171	C$_{26}$H$_{34}$N$_2$O$_5$S· 2HCl	55.81 (55.92	6.49 6.54	5.01 5.04)
trans-18b	7-OCH$_3$	N⬡N–Ph	4	C	11	128—130	C$_{26}$H$_{34}$N$_2$O$_5$S	64.17 (64.32	7.04 6.95	5.76 5.62)
cis-19b	7-OCH$_3$	N⬡N–Ph	5	C	22	125—128	C$_{27}$H$_{36}$N$_2$O$_5$S· HCl·1^1/$_2$H$_2$O	57.48 (57.20	7.14 6.98	4.97 4.94)
cis-20b	7-OCH$_3$	N⬡N–◯Cl	3	C	55	145—150	C$_{25}$H$_{31}$ClN$_2$O$_5$S· 2HCl·1/2H$_2$O	50.98 (50.67	5.82 6.12	4.76 4.61)
trans-20b	7-OCH$_3$	N⬡N–◯Cl	3	C	33	111—113	C$_{25}$H$_{31}$ClN$_2$O$_5$S·	59.22 (59.28	6.16 6.27	5.52 5.34)
cis-21b	7-OCH$_3$	N⬡N–◯OCH$_3$	3	C	50	140—145	C$_{26}$H$_{34}$N$_2$O$_6$S· HCl·2H$_2$O	54.30 (54.57	6.83 6.64	4.87 4.70)
trans-21b	7-OCH$_3$	N⬡N–◯OCH$_3$	3	C	20	170—175	C$_{26}$H$_{34}$N$_2$O$_6$S· 2HCl·H$_2$O	52.61 (52.99	6.45 6.24	4.72 4.72)
cis-22b	7-OCH$_3$	N⬡N–◯OCH$_3$ (OCH$_3$)	3	C	55	185—193	C$_{26}$H$_{34}$N$_2$O$_6$S· 2HCl	54.26 (54.56	6.30 6.29	4.87 5.07)
trans-22b	7-OCH$_3$	N⬡N–◯OCH$_3$ (OCH$_3$)	3	C	22	178—182	C$_{26}$H$_{34}$N$_2$O$_6$S· 2HCl	54.26 (54.05	6.31 6.36	4.88 4.66)
cis-23b	7-CH$_3$	N⬡N$\langle$Ph/Ph	3	C	65	133—135	C$_{32}$H$_{38}$N$_2$O$_5$S	68.30 (68.48	6.81 6.73	4.98 4.97)

The header for Analysis columns: **Analysis (%) Calcd (Found)** spanning C, H, N.

TABLE I. (continued)

Compd. No.	R_1	$N<^{R_2}_{R_3}$	n	Method[a]	Yield (%)	mp (°C)	Formula	Analysis (%) Calcd (Found)		
								C	H	N
trans-23b	7-OCH₃	N◯N-CH(Ph)(Ph)	3	C	33	173—176	$C_{32}H_{38}N_2O_5S$	68.30 (68.34	6.81 6.81	4.98 4.82)
cis-24b	7-OCH₃	N◯N-⟨O/N⟩	3	C	63	173—176	$C_{24}H_{31}N_3O_5S \cdot 2HCl \cdot 1/2H_2O$	51.89 (51.96	6.17 6.40	7.56 7.32)
trans-24b	7-OCH₃	N◯N-⟨O/N⟩	3	C	25	222—225	$C_{24}H_{31}N_3O_5S \cdot 2HCl$	52.74 (52.31	6.09 6.02	7.69 7.65)
cis-25b	7-OCH₃	N◯-Ph	3	D	51	135—140	$C_{26}H_{33}NO_5S \cdot HCl \cdot 1/2H_2O$	60.39 (60.48	6.82 6.84	2.71 2.70)
cis-26b	7-OCH₃	N◯N-⟨O⟩-F	3	D	36	140—150	$C_{25}H_{31}FN_2O_5S \cdot 2HCl \cdot 1/2H_2O$	52.44 (52.71	5.90 5.82	4.89 4.79)
cis-27b	7-OCH₃	N◯-CO-⟨O⟩-F	3	D	43	150—153	$C_{27}H_{32}FNO_6S \cdot HCl \cdot H_2O$	56.68 (56.71	6.17 6.08	2.45 2.46)
cis-28b	7-OCH₃	N◯N-⟨O/N,N⟩	3	D	24	210—213	$C_{23}H_{30}N_4O_5S \cdot 2HCl \cdot H_2O$	48.85 (48.94	6.06 5.84	9.91 9.99)
cis-29b	7-OCH₃	N◯N-CH₃	3	D	35	142—145	$C_{20}H_{30}N_2O_5S \cdot 1/2H_2O$	57.29 (57.45	7.45 7.40	6.68 6.71)
cis-30b	7-OCH₃	N◯O	3	D	47	205—210	$C_{19}H_{29}NO_6S \cdot HCl$	52.59 (52.57	6.50 6.72	3.23 3.19)
cis-31b	7-OCH₃	NEt₂	3	D	34	185—188	$C_{19}H_{29}NO_5S \cdot HCl$	54.34 (54.07	7.20 7.23	3.34 3.34)
cis-32b	7-OCH₃	N(CH₃)-(CH₂)₂-⟨O⟩(OCH₃)₂	3	D	41	—[b]	$C_{26}H_{35}NO_7S \cdot HCl \cdot 1/2H_2O$	56.67 (56.68	6.77 6.97	2.54 2.51)
cis-33b	7-OCH₃	N◯N-⟨O⟩(OH)	3	D	50	175—190	$C_{25}H_{32}N_2O_6S \cdot 2HCl \cdot 1/2H_2O$	52.63 (52.91	6.18 5.94	4.91 4.95)
cis-34b	7-OCH₃	N◯N-⟨O⟩(OH)	3	D	65	175—180	$C_{25}H_{32}N_2O_6S \cdot 2HCl \cdot H_2O$	51.81 (52.00	6.26 6.02	4.83 4.72)
cis-35b	7-OCH₃	N◯N-⟨O⟩-OH	3	D	50	240—245	$C_{25}H_{32}N_2O_6S \cdot 2HCl$	53.43 (53.20	6.10 5.97	4.99 5.21)
cis-36f	7-OCH₂Ph	N◯N-⟨O⟩-OH	3	D	57	247—251	$C_{31}H_{36}N_2O_6S \cdot HCl$	61.93 (61.91	6.20 6.01	4.66 4.65)
cis-37f	7-OCH₂Ph	N◯NH	3	F	64	193—200	$C_{25}H_{32}N_2O_5S \cdot 2HCl \cdot 1/2H_2O$	54.15 (54.10	6.36 6.30	5.05 5.11)
cis-38g	7-OH	N◯N-⟨O⟩-OH	3	E	72	226—229	$C_{24}H_{30}N_2O_6S$	60.74 (60.47	6.37 6.39	5.90 5.71)
cis-39g	7-OH	N◯NH	3	E	90	233—240	$C_{18}H_{26}N_2O_5S \cdot 2HCl$	47.47 (47.19	6.20 6.36	6.15 5.86)

a) Method E, catalytic reduction of the corresponding O-benzyl ether. Method F, see experimental section. b) Amorphous powder.

benzoxathiepin-4-carboxylates (1a—f) by alkylation of the reactive methine carbon (Chart 2). The ketoesters (1a—f) were alkylated with ω-halogenoalkyl bromides having a side chain of various lengths ($n=3$—5) in refluxing acetonitrile by using potassium carbonate and a catalytic amount of potassium iodide to yield a mixture of the desired C-alkylated compounds (30—40%) and O-alkylated enole ethers (10—20%) as a by-product. Chromatographic separation of the reaction mixture gave methyl 4-(ω-halogenoalkyl)-3-oxo-3,4-dihydro-2H-1,5-benzoxathiepin-4-carboxylates (2—4). The 4-[2-oxo-2-(4-phenyl-1-piperazinyl)ethyl] derivative (5b) was prepared by alkylation of 1b with 1-chloroacetyl-4-phenylpiperazine in 69% yield. Conversion of the halogeno moiety of 2—4 into the amino group by sub-

stitution with some amines was carried out by heating in N,N-dimethylformamide (DMF) at 70 °C in the presence of potassium carbonate and potassium iodide to give methyl 4-aminoalkyl-substituted 3-oxo-3,4-dihydro-2H-1,5-benzoxathiepin-4-carboxylates (7—14) in fairly good yields (58—76%) (method A). Direct introduction of an N-phenyl-piperazinylpropyl moiety into the 4-position of 1 by alkylation using 4-phenyl-1-pipera-zinylpropyl chloride gave N-phenylpiperazinylpropyl derivatives (7a—e) in 18—31% yields (method B). Reduction of 7—14 with sodium borohydride (NaBH$_4$) in an ice-cooled so-lution of methanol and tetrahydrofuran (THF), and subsequent separation of the resulting stereoisomeric products by column chromatography on silica gel gave methyl cis- and trans-4-aminoalkyl-3-hydroxy-3,4-dihydro-2H-1,5-benzoxathiepin-4-carboxylates (17—24) (method C) (Table I). The configurational nomenclature in this paper refers to the relative con-figuration between the 3-hydroxy group and the 2- or 4-substituent with higher priority. In each case, NaBH$_4$ reduction produced predominantly cis-alcohols over trans-isomers in the range of 1:1—2:1 ratios. Similar NaBH$_4$ reduction of 2b and 2f afforded cis-4-chloropropyl-3-ols (cis-15b, 63% and cis-15f, 50%) and trans-alcohols (trans-15b, 25% and trans-15f, 30%), respectively. Substitution of cis-15b and cis-15f with various kinds of amines gave cis-alcohols with a modified amino group (cis-25—cis-36) (method D). The N-phenylpiperazinylethyl derivative (cis-16b) was synthesized by NaBH$_4$ reduction of 5b, followed by selective reduction of the amide moiety with sodium monoacetoxyborohydride[10] in boiling THF. 7-Hydroxy derivatives (cis-17g, cis-36g, and cis-39g) were obtained by catalytic reduction of the corresponding 7-benzyloxy derivatives (cis-17f, cis-36f, and cis-37f) using palladium black as a catalyst in ethanol containing hydrochloric acid (method E). The stereochemistries of the compounds bearing substituents at the 3- and 4-positions were determined on the basis of various data including X-ray crystallographic analysis, proton nuclear magnetic resonance (^{1}H-NMR) spectral data and Rf values of each stereoisomer. The physicochemical properties of methyl cis- and trans-4-aminoalkyl-3-hydroxy-3,4-dihydro-2H-1,5-benzoxathiepin-4-carboxylates (16—39) thus obtained are summarized in Table I.

The N-phenylpiperazinylpropyl group was introduced into the 2-position by converting the ester group of methyl 3-(3-oxo-3,4-dihydro-2H-1,5-benzoxathiepin-2-yl)propionates (40b and 40c)[11] in three steps (Chart 3). Reduction of 40b with NaBH$_4$ and subsequent chromatographic separation gave cis-41b (47%) and trans-41b (36%). On the other hand, similar reduction of 40c gave cis-41c (86%) and a minor product (7%) which could not be

40b : R$_1$=7-OCH$_3$
40c : R$_1$=8-OCH$_3$

41b : R$_1$=7-OCH$_3$; R=OCH$_3$
41c : R$_1$=8-OCH$_3$; R=OCH$_3$

42b : R$_1$=7-OCH$_3$; R=N N-Ph

42c : R$_1$=8-OCH$_3$; R=N N-Ph

43b : R$_1$=7-OCH$_3$
43c : R$_1$=8-OCH$_3$
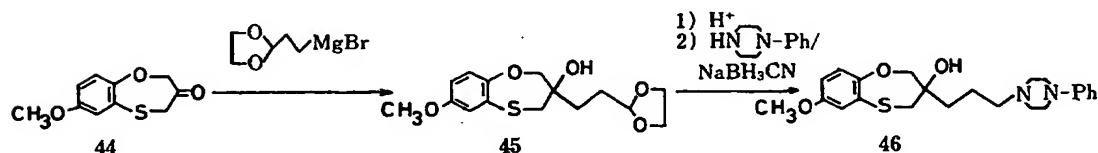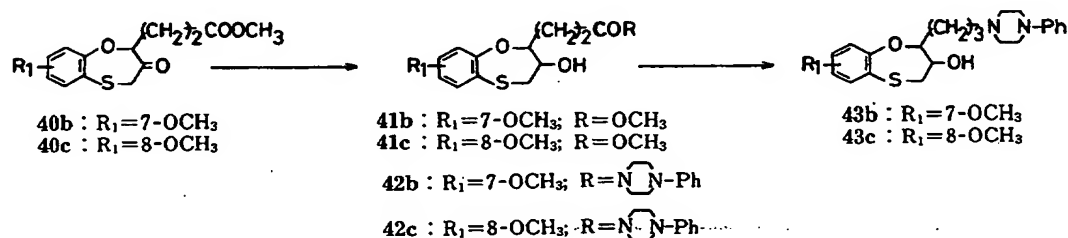
1) H$^+$
2) HN N-Ph/
NaBH$_3$CN

Chart 3

identified as *trans*-**41c**. Heating a mixture of the ester (*cis*-**41b**) and *N*-phenylpiperazine at 90 °C for 5 h afforded the amide (*cis*-**42b**), which was reduced with lithium aluminum hydride (LiAlH$_4$) in THF to yield *cis*-7-methoxy-2-[3-(4-phenyl-1-piperazinyl)propyl]-3,4-dihydro-2*H*-1,5-benzoxathiepin-3-ol (*cis*-**43b**). Similarly, *trans*-**43b** and *cis*-**43c** were prepared *via* the amides (*trans*-**42b** and *cis*-**42c**).

Grignard reaction of 7-methoxy-3,4-dihydro-2*H*-1,5-benzoxathiepin-3-one (**44**)[11] with 2-(1,3-dioxolan-2-yl)ethylmagnesium bromide[11] in THF gave 3-(1,3-dioxolan-2-yl)ethyl-7-methoxy-3,4-dihydro-2*H*-1,5-benzoxathiepin-3-ol (**45**) in 82% yield. Next, deprotection of the acetal group to aldehyde by treatment with dilute hydrochloric acid and subsequent reductive amination with *N*-phenylpiperazine using sodium cyanoborohydride afforded 7-methoxy-3-[3-(4-phenyl-1-piperazinyl)propyl]-3,4-dihydro-2*H*-1,5-benzoxathiepin-3-ol (**46**) in 57% yield (Chart 3).

The compound (**50b**) lacking the 4-methoxycarbonyl group in *cis*-**17b**, which showed the most potent antagonistic activity against S$_2$-receptors, was prepared in several steps from **2b** as illustrated in Chart 4. Heating **2b** in DMF at 100 °C for 6 h in the presence of aqueous lithium chloride afforded 4-(3-chloropropyl)-7-methoxy-3,4-dihydro-2*H*-1,5-benzoxathiepin-3-one (**47b**) in 48% yield. Either NaBH$_4$ reduction of **47b** and subsequent replacement of the chloro group by *N*-phenylpiperazine or initial amination of **47b** and subsequent NaBH$_4$ reduction gave the same single product, the structure of which was confirmed as the *cis*-isomer (*cis*-**50b**) by X-ray crystallographic analysis. In order to prepare the *trans*-isomer, we examined another synthetic route and found that decarboxylation of *cis*-4-(3-chloropropyl)-3-hydroxy-7-methoxy-3,4-dihydro-2*H*-1,5-benzoxathiepin-4-carboxylic acid (*cis*-**51b**) obtained by alkaline hydrolysis of *cis*-**15b** with heating at 180 °C for 30 min gave *trans*-**48b** with stereochemical retention of the 3-hydroxy and 4-(3-chloropropyl) groups in 16% yield. Subsequent substitution reaction of *trans*-**48b** with *N*-phenylpiperazine gave *trans*-**50b**.
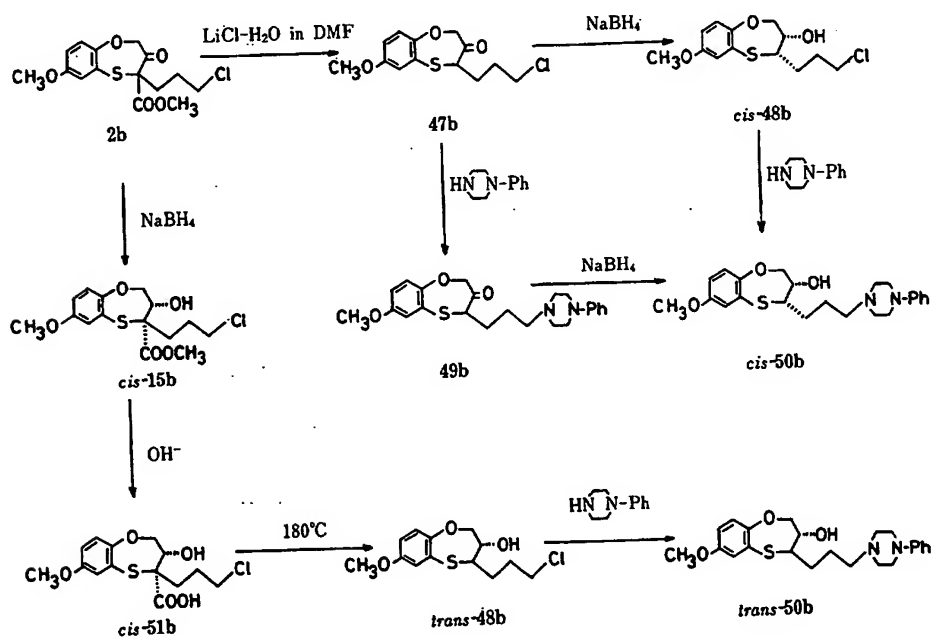

Chart 4

Removal of the 3-hydroxy group from *cis*-17b was unsuccessful. Tosylation of *cis*-17b with tosyl chloride in pyridine and subsequent catalytic reduction of the crude product using 10% palladium charcoal in ethyl acetate yielded two isomeric products (52 and 53) which were also obtained by reduction of *cis*-15b with red phosphorus and hydriodic acid in aqueous acetic acid, followed by treatment with N-phenylpiperazine. The infrared (IR) spectra of 52 and 53 showed similar absorptions to each other. The 400 MHz NMR spectrum of 52 exhibited two double doublets at δ 4.115 ($J = 12.0$, 5.4 Hz) and 4.263 ($J = 12.0$, 2.1 Hz) due to methylenic protons adjacent to the oxygen atom and a sextet (ddd) at δ 3.612 ($J = 2.1$, 5.4, 9.5 Hz) assignable to the methine proton attached to the carbon bearing the sulfur atom. On irradiation at δ 3.612, the two double doublets were transformed into two doublets with geminal coupling ($J = 12.0$ Hz). The ^{1}H-NMR spectrum of 53 showed similar signals with ABX coupling at δ 4.184 (1H, dd, $J = 12.2$, 2.0 Hz), 4.439 (1H, dd, $J = 12.2$, 4.2 Hz), and 3.599 (1H, ddd, $J = 2.1$, 4.2, 9.8 Hz). These results indicate the presence of the OCH_2CHS group and the absence of the OCH_2CH_2 group as partial structures of 52 and 53. Thus, the structures of 52 and 53 were assigned as isomeric methyl 5-(4-phenyl-1-piperazinyl)-2-(6-methoxy-1,4-benzoxathian-3-yl)pentanoates, which might be produced by rearrangement involving the episulfonium ion intermediates[12] generated by elimination of the hydroxy group at the 3-position. Compound 58, which lacks the 3-hydroxy group in addition to the 4-ester of *cis*-17b, was synthesized as illustrated in Chart 5. Grignard reaction of 3-chloropropanal with 2-(1,3-dioxolan-2-yl)ethylmagnesium bromide in THF gave 1-chloro-5-(1,3-dioxolan-2-yl)pentan-3-ol (54) in 73% yield. Then 54 was converted into 5-(1,3-dioxolan-2-yl)-3-mesyloxypentyl benzoate (55) by the reaction of 54 with sodium benzoate in DMF, followed by mesylation.
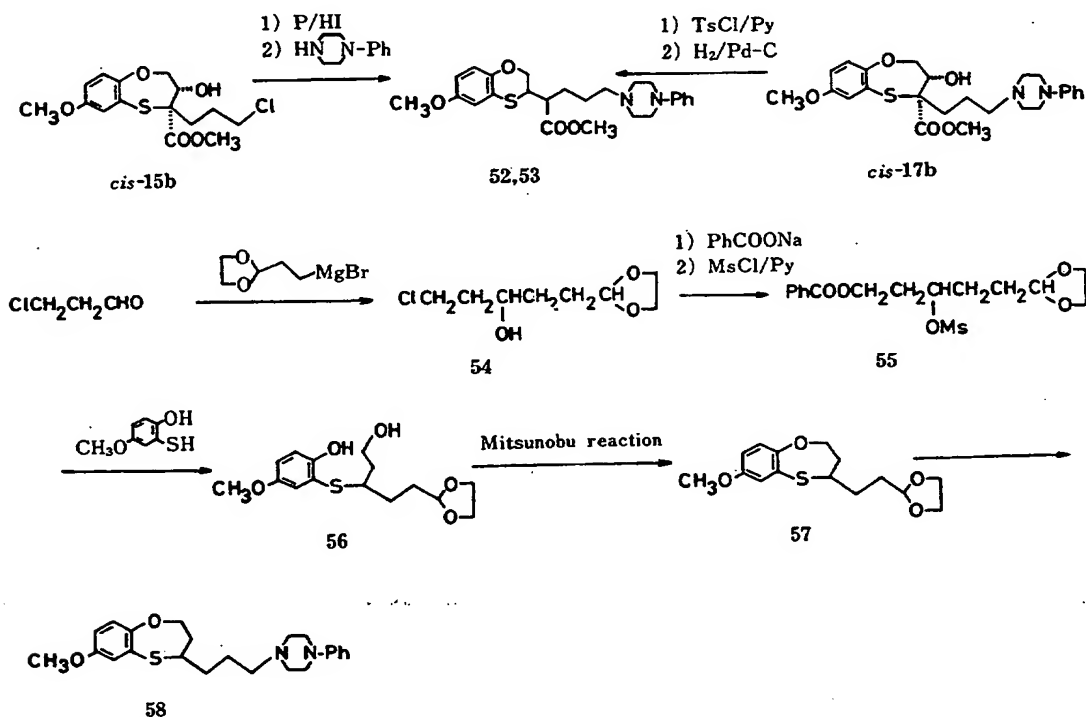

Chart 5

Treatment of **55** with 4-methoxy-2-mercaptophenol and subsequent alkaline hydrolysis gave the precursor (**56**) in 43% yield from **55**. Ring closure of **56** was conducted by means of the Mitsunobu reaction[13] using triphenylphosphine and ethyl azodiformate in toluene to afford 7-methoxy-4-[2-(1,3-dioxolan-2-yl)ethyl]-3,4-dihydro-2H-1,5-benzoxathiepin (**57**, 71%), which was converted into the desired 7-methoxy-4-[3-(4-phenyl-1-piperazinyl)propyl]-3,4-dihydro-2H-1,5-benzoxathiepin (**58**, 51%) by reductive amination after deprotection of the acetal group of **57**.

Modifications of the 3-hydroxy and the 4-ester groups of cis-**17b** were done by O-acetylation, O-carbamoylation using methyl isocyanate, alkaline hydrolysis, esterification of the resulting 4-carboxylic acid with diethyl sulfate, and lithium aluminum hydride reduction, to give the O-acetate (cis-**59b**), the 3-N-methylcarbamoyloxy derivative (cis-**60b**), 4-carboxylic acid (cis-**61b**), the 4-ethyl ester (cis-**62b**) and the 4-methanol (cis-**63b**), respectively (Chart 6).

cis-**59b**   cis-**60b**   cis-**61b**

cis-**62b**   cis-**63b**
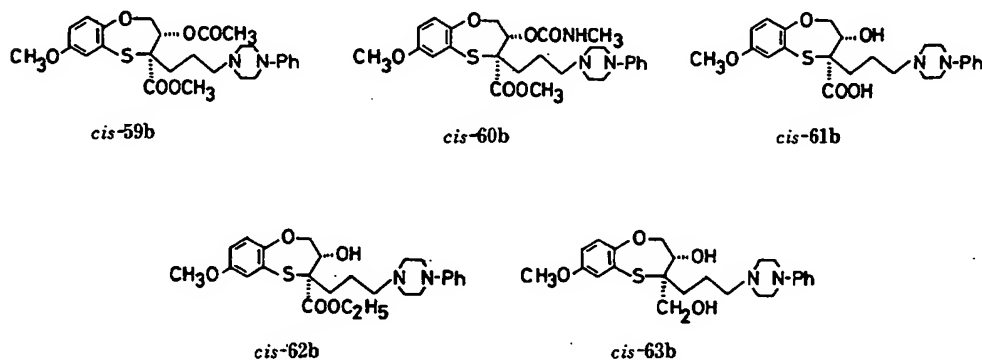
Chart 6

We also tried to prepare the 1-benzoxepin and 1-benzothiepin analogs of cis-**17b** in order to clarify the pharmacological significance of the hetero atoms in the 1,5-benzoxathiepin ring (Chart 7). Methyl 8-methoxy-3-oxo-2,3,4,5-tetrahydro-1-benzoxepin-2-carboxylate (**64**) was obtained by Dieckmann reaction of methyl 3-(4-methoxy-2-methoxycarbonylmethyl-oxy)phenylpropionate according to the method described by Huckle et al.[14] Methyl 3-oxo-2,3,4,5-tetrahydro-1-benzothiepin-2-carboxylates (**65** and **66**) were prepared by similar Dieckmann reaction according to the procedure of Huckle et al.[14] via the Newman's reaction[15] of methyl 2-hydroxyphenylpropionates. The syntheses of N-phenylpiperazinyl-propyl-substituted 1-benzoxepin and 1-benzothiepin derivatives (**73**, **74**, and **75**) from the ketoesters (**64**, **65**, and **66**) were done by methods similar to those described for 1,5-benzoxathiepin derivatives, involving alkylation with 3-bromo-1-chloropropane, subsequent NaBH$_4$ reduction and finally substitution with N-phenylpiperazine (Chart 7) (Table II).

64   67   70   73
65   68   71   74
66   69   72   75

64, 67, 70, 73:   R$_1$=OCH$_3$; X=O
65, 68, 71, 74:   R$_1$=H; X=S
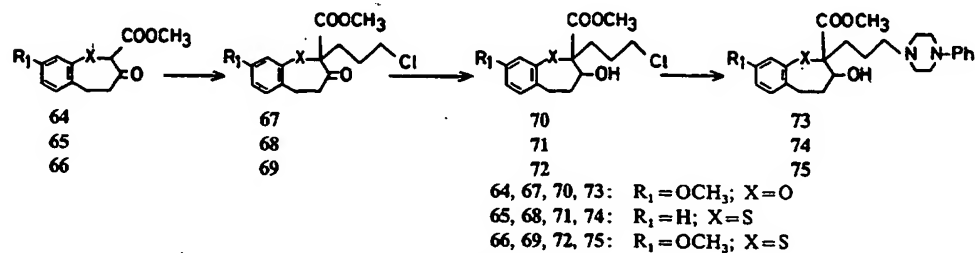66, 69, 72, 75:   R$_1$=OCH$_3$; X=S

Chart 7

TABLE II. Physicochemical Properties of N-Phenylpiperazinylpropyl-Substituted 1-Benzoxepin and 1-Benzothiepin Derivatives (73—75)

Compd. No.	R_1	X	Yield (%)	mp (°C)	Formula	Analysis (%) Calcd (Found)		
						C	H	N
cis-73	OCH_3	O	47	126—128	$C_{26}H_{34}N_2O_5$	68.70 (68.42	7.54 7.62	6.16 6.02)
trans-73	OCH_3	O	72	140—155	$C_{26}H_{34}N_2O_5 \cdot$ 2HCl	59.20 (59.12	6.88 6.96	5.31 5.23)
cis-74	H	S	60	152—154	$C_{25}H_{32}N_2O_3S$	68.15 (68.40	7.32 7.34	6.36 6.36)
cis-75	OCH_3	S	80	145—150	$C_{26}H_{34}N_2O_4S \cdot$ $HCl \cdot 1/2\,H_2O$	60.51 (60.39	7.03 7.36	5.43 5.49)

cis-17b·HCl (CV-5197)[a]   cis-50b   cis-73
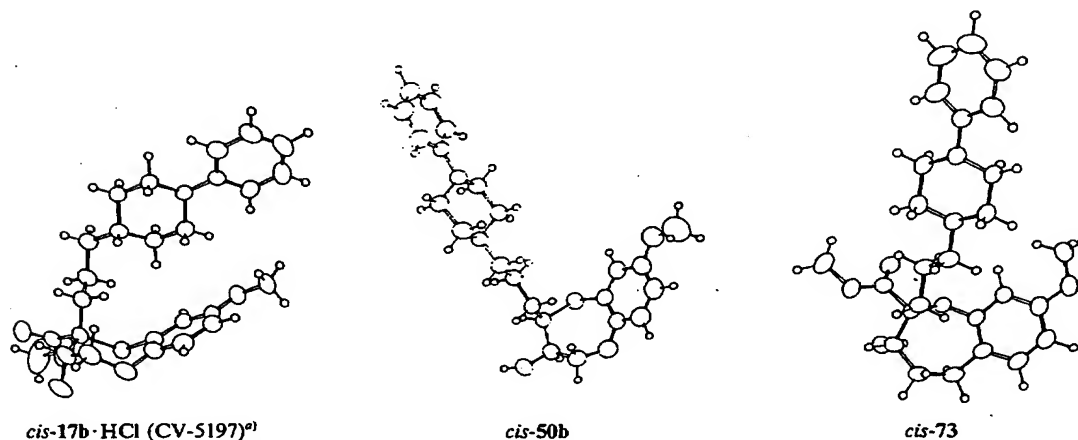
Fig. 1. X-Ray Structures of cis-17b·HCl, cis-50b, and cis-73
a) Shown without Cl⁻.

In the case of 1-benzothiepin derivatives, the hydride reduction of the 3-carbonyl moiety gave exclusively cis-alcohols (cis-71 and cis-72) without detectable stereoisomers on thin-layer chromatography (TLC). The configurations of these compounds were determined by X-ray chrystallographic analysis of cis-71 and comparison of the 400 MHz NMR spectral data of the products (71 and 72).

Configurations and Conformations of 1,5-Benzoxathiepin Derivatives and R lated Compounds

The conformations of seven-membered compounds have been investigated theoretically and experimentally from the viewpoint of interconversion and pseudorotation.[16,17]

We first determined the configurations of cis-17b, cis-50b, cis-58b, cis-71, and cis-73 by X-ray crystallographic analysis and then examined the conformations in solution based on 400 MHz NMR spectra data. The X-ray results have shown that the chair form of the seven-membered ring is the common conformation for 1,5-benzoxathiepin (cis-17b, cis-50b, and cis-58b), 1-benzoxepin (cis-73), and 1-benzothiepin (cis-71) derivatives (Fig. 1). The most striking

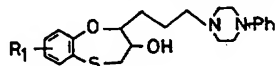TABLE. III. Selected 400 MHz NMR Spectral Data for 4-(4-Phenyl-1-piperazinyl)alkyl-3,4-dihydro-2H-1,5-benzoxathiepin-3-ols
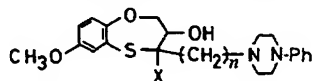
Compd. No.	X	n	Salt	NMR (DMSO-d_6)[a]					
				Chemical shift δ (ppm)			Coupling constant (Hz)		
				C_2-H_a	C_2-H_b	C_3-H	$J_{2a,3}$	$J_{2b,3}$	$J_{3,4}$
cis-16b	COOCH$_3$	2	2HCl	4.022	4.168	4.080	2.7	6.1	—
cis-17b	COOCH$_3$	3	HCl	3.873	4.155	3.999	0—1.0	4.6	—
cis-17b	COOCH$_3$	3	Free base	3.843	4.249	4.078	0—1.0	3.4	—
trans-17b	COOCH$_3$	3	HCl	3.794	4.107	4.383	8.4	3.8	—
cis-18b	COOCH$_3$	4	2HCl	3.920	4.151	4.017	2.3	5.6	—
trans-18b	COOCH$_3$	4	2HCl	3.783	4.063	4.314	7.8	3.7	—
cis-19b	COOCH$_3$	5	HCl	3.913	4.149	4.011	2.3	5.5	—
cis-50b	H	3	2HCl	3.776	4.017	4.152	8.5	3.8	3.8[b]
trans-50b	H	3	2HCl	3.855	4.329	3.785	4.9	2.8	7.7[c]

a) cis-17b (free base) was determined in CDCl$_3$ solution. b) δ 3.206 ppm (C$_4$-H). c) δ 3.031 ppm (C$_4$-H).

TABLE IV. Selected 400 MHz NMR Spectral Data for 2-[3-(4-Phenyl-1-piperazinyl)propyl]-3,4-dihydro-2H-1,5-benzoxathiepin-3-ols

Compd. No.	R$_1$	NMR (CDCl$_3$)						
		Chemical shift δ (ppm)				Coupling constant (Hz)		
		C_2-H	C_3-H	C_4-H_a	C_4-H_b	$J_{2,3}$	$J_{3,4a}$	$J_{3,4b}$
cis-43b	7-OCH$_3$	3.609	3.975	2.953	3.039	0—1.0	2.1	5.4
trans-43b	7-OCH$_3$	3.96	3.96	2.735	3.534	—[a]	4.8	2.3
cis-43c	8-OCH$_3$	3.668	3.970	2.886	2.966	0—1.0	2.1	5.4

a) Not determined.

characteristic of cis-17b is the folded conformation of the whole molecule and the quasi-axial orientation of the sterically bulky N-phenylpiperazinylpropyl substituent. The 400 MHz NMR spectral data of the 4-[3-(4-phenyl-1-piperazinyl)propyl]-3-hydroxy-3,4-dihydro-2H-1,5-benzoxathiepin derivatives also support the occurrence of solution conformations that are similar to the solid state conformations, except in the case of trans-50b (Table III). The rather large coupling constant in trans-17b ($J_{2a,3}$ = 8.4 Hz) suggests the presence of a quasi-equatorial 3-hydroxy group in trans-17b, while the small values in cis-17b ($J_{2a,3}$ = 0—1.0 Hz and $J_{2b,3}$ = 4.6 Hz) indicate a major contribution of a conformation similar to the X-ray conformation in solution. The excellent agreement of the correlative J values of cis-50b and trans-17b indicates that these compounds possess similar conformations except for the structural difference of the absence or presence of the 4-ester moiety. However, the discrepancy between the J values in the NMR spectral data of trans-50b and cis-17b suggests that the major conformer of trans-50b differs from the X-ray conformer of cis-17b. The $J_{3,4}$

TABLE V. Biological Activities of Methyl 4-Aminoalkyl-3-hydroxy-3,4-dihydro-
2H-1,5-benzoxathiepin-4-carboxylates

$$\text{R}_1\text{—}\underset{\text{OH}}{\overset{\text{COOCH}_3}{\underset{\big|}{\overset{\big|}{\text{C}}}}}\text{—(CH}_2)_n\text{—NR}_2\text{R}_3\quad\left[\begin{array}{c}\text{S}\\\text{O}\end{array}\right]$$

Compd. No.	R_1	N:R_2/R_3	n	Serotonin S_2-blocking activity[a]			Adrenaline α_1-blocking activity[b]	
				10^{-5}	10^{-6}	10^{-7} M	10^{-5}	10^{-6} M
cis-16b	7-OCH$_3$	N–N-Ph	2	89			80	
cis-17a	H	N–N-Ph	3	100	77	3	100	30
trans-17a	H	N–N-Ph	3	100	18		100	75
cis-17b	7-OCH$_3$	N–N-Ph	3	100	77		5	
trans-17b	7-OCH$_3$	N–N-Ph	3	100	89	15	66	
cis-17c	8-OCH$_3$	N–N-Ph	3	92	71	3	31	
trans-17c	8-OCH$_3$	N–N-Ph	3	96	28		53	
cis-17d	7-Cl	N–N-Ph	3	100	58	31	45	
trans-17d	7-Cl	N–N-Ph	3	100	67	12	70	
cis-17e	7-CH$_3$	N–N-Ph	3	100	77	40	35	
trans-17e	7-CH$_3$	N–N-Ph	3	100	27	0	58	
cis-17g	7-OH	N–N-Ph	3	79	91		0	
cis-18b	7-OCH$_3$	N–N-Ph	4	66			95	
trans-18b	7-OCH$_3$	N–N-Ph	4	66	35		90	
cis-19b	7-OCH$_3$	N–N-Ph	5	56			90	
cis-20b	7-OCH$_3$	N–N—⟨Cl⟩	3	94	35		47	
cis-21b	7-OCH$_3$	N–N—⟨OCH$_3$⟩	3	88	12		100	28
cis-24b	7-OCH$_3$	N–N—⟨N⟩	3	100	77	55	100	18
cis-25b	7-OCH$_3$	N–N–Ph	3	100	88	25	40	
cis-26b	7-OCH$_3$	N–N—⟨F⟩	3	100	66	12	30	
cis-27b	7-OCH$_3$	N–N—CO⟨F⟩	3	100	88	50	100	
cis-28b	7-OCH$_3$	N–N—⟨N=N / OCH$_3$⟩	3	68			0	
cis-32b	7-OCH$_3$	N(CH$_2$)$_2$—⟨OCH$_3$ / OCH$_3$⟩	3	83	27		15	
cis-33b	7-OCH$_3$	N–N—⟨OH⟩	3	100	12		55	
cis-34b	7-OCH$_3$	N–N—⟨OH⟩	3	100	36	16	10	
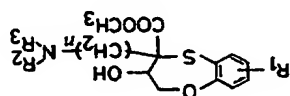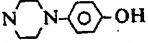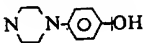
TABLE V. (continued)

Compd. No.	R_1	$N\begin{smallmatrix}R_2\\R_3\end{smallmatrix}$	n	Serotonin S_2-blocking activity[a]			Adrenaline α_1-blocking activity[b]	
				10^{-5}	10^{-6}	10^{-7} M	10^{-5}	10^{-6} M
cis-35b	7-OCH$_3$	N◯N-⟨O⟩-OH	3	100	100	79	56	
cis-38g	7-OH	N◯N-⟨O⟩-OH	3	100	0		8	

a) % inhibition of 5-HT-induced contraction in pig coronary artery. *b*) % inhibition of norepinephrine-induced contraction in rabbit aorta.

TABLE VI. Biological Activities of 3-(4-Phenyl-1-piperazinyl)propyl-Substituted 3,4-Dihydro-2H-1,5-benzoxathiepin Derivatives and Related Analogs

Compd. No.	Serotonin S_2-blocking activity[a]			Adrenaline α_1-blocking activity[b]
	10^{-5}	10^{-6}	10^{-7} M	10^{-5} M
7b	100	80	2	63
cis-43b	56	13		50
trans-43b	42	0		77
cis-43c	100	63		53
46	25	0		99
cis-50b	99	35		50
trans-50b	72			55
58	58			60
cis-59b	100	92	19	40
cis-60b	100	47		72
cis-62b	100	83	19	0
cis-63b	90	17	0	50
cis-73	100			44
trans-73	100	24		62
cis-74	96	60		36
cis-75	100	69		31

a) % inhibition of 5-HT-induced contraction in pig coronary artery. *b*) % inhibition of norepinephrine-induced contraction in rabbit aorta.

value (7.7 Hz) of trans-50b suggests a substantial contribution of quasi-equatorial orientation of the N-phenylpiperazinylpropyl group at the 4-position. In the case of the derivatives with a side chain of various lengths (16, 18 and 19), it was deduced that the main conformation of each stereoisomer was similar to that found for the corresponding isomer of 17b on the basis of the NMR spectral data, supposing the half-chair conformation for the seven-membered ring. On the other hand, the equatorial orientation of the N-phenylpiperazinylpropyl moiety at the 2-position was estimated from the NMR spectral data of cis-43b, c and trans-43b (Table IV). X-ray crystallographic analyses and the NMR spectral data of 1-benzoxepin (73) and 1-benzothiepin (74 and 75) derivatives indicated that these compounds also had major conformers similar to those observed in 17b. The main contribution of trans-1,2-diaxial orientation of the sterically bulky substituents for cis-17b in contrast with trans-50b is readily rationalizable in terms of the stabilizing effect associated with the favorable hydrogen bonding between the 3-hydroxy function and the 4-ester carbonyl in cis-17b compared with

trans-**50b**, lacking the ester group.

Biological Results and Discussion

The S_2-receptor-blocking activity and selectivity toward S_2-receptors over adrenergic α_1-receptors of the aminoalkyl-substituted 1,5-benzoxathiepin derivatives and related compounds synthesized in this paper were evaluated in terms of ability to antagonize serotonin-induced contraction in the isolated pig coronary artery and to block norepinephrine-induced contraction in the isolated rabbit aorta. The results of *in vitro* evaluation are shown in Tables V and VI.

Methyl 4-aminoalkyl-3-hydroxy-3,4-dihydro-2*H*-1,5-benzoxathiepin-4-carboxylates showed significant S_2-receptor-blocking activities. The inhibitory potency for serotonin-induced contraction increased in the order of 3>2, 4>5 of side chain length (*n*). The substituents on the benzene ring of the 1,5-benzoxathiepin skeleton also influenced the biological activities. Introduction of the methoxy group into the 7-position (**17b**) resulted in marked enhancement of the activity, whereas shift of the methoxy group from the 7- to the 8-position diminished the effect. Substituents of the amino group in the side chain also caused changes (**17b,20b—35b**) in the structure–activity relationships. The nitrogen atom attached to the 4-propyl group might play an important role in the interaction with S_2-receptors since the 4-phenylpiperidyl derivative (*cis*-**25b**) showed activity comparable to that of the *N*-phenylpiperazinyl derivative (*cis*-**17b**). The presence of the aromatic ring within a distance of two or three methylenic chains from the nitrogen atom described above seemed to be preferable for S_2-receptor-blocking activity. Among the stereochemical isomers, the *cis*-isomers, rather than the *trans*-isomers, showed more potent and more selective antagonism toward S_2-receptors over adrenergic α_1-receptors. When the 3-(4-phenyl-1-piperazinyl)propyl moiety was introduced into the 2-position, the presence of the methoxy group at the 8-position (*cis*-**43c**) instead of the 7-position (**43b**) was critical for the manifestation of biological activities. On the other hand, substitution of the 3-(4-phenyl-1-piperazinyl)propyl group at the 3-position (**46**) resulted in a marked reduction of S_2-receptor-blocking activity and considerably increased inhibitory potency for adrenergic α_1-receptors. In the series of methyl aminoalkyl-substituted 3-hydroxy-3,4-dihydro-2*H*-1,5-benzoxathiepin-4-carboxylates, methyl *cis*-3-hydroxy-7-methoxy-4-[3-(4-phenyl-1-piperazinyl)propyl]-3,4-dihydro-2*H*-1,5-benzoxathiepin-4-carboxylate hydrochloride (*cis*-**17b**, CV-5197) showed the most potent S_2-receptor-blocking activity and the highest selectivity over the adrenergic α_1-blocking activity. Some modifications of the 3-hydoxy and 4-ester groups of *cis*-**17b** gave the following results. The activities were unchanged upon modifications of the 3-hydroxy group, *e.g.*, *O*-acetate (*cis*-**59b**) and *N*-methylcarbamoyloxy (*cis*-**60b**) derivatives and the 3-carbonyl compound (**7b**). Removal of the 4-ester moiety gave quite different results in different stereochemical isomers. The *cis*-isomer (*cis*-**50b**) showed activities comparable to those of *trans*-**17b**. However, the S_2-receptor-blocking activity of *trans*-**50b** was 100 times less potent than that of *cis*-**17b** in spite of the configurational retention of the 3-hydroxy and 4-aminoalkyl moieties in both molecules. Removal of the 3-hydroxy and 4-ester groups (**58**) resulted in further reduction of the activity. Ring-contraction of 1,5-benzoxathiepin skeleton (**52** and **53**) resulted in loss of S_2-receptor antagonistic activity. In the series of skeletal modifications, methyl *cis*-3-hydroxy-2-[3-(4-phenyl-1-piperazinyl)propyl]-2,3,4,5-tetrahydro-1-benzothiepin-2-carboxylate (*cis*-**74**) showed almost equipotent activity to the corresponding 1,5-benzoxathiepin derivative (*cis*-**17a**). However, introduction of the methoxy group (*cis*-**75**) did not produce the potentiation of the activity that was observed in the case of the 1,5-benzoxathiepins (**17a→17b**), and the inhibitory potency of the 1-benzoxepin derivative (*cis*-**73**) was 10 times less than that of *cis*-**17b** in spite of the conformational similarity between the two compounds (Fig. 1). These results suggest that the oxygen atom in the 1,5-benzoxathiepin ring of *cis*-**17b**

might also play a significant role in the interaction with S_2-receptors.

X-Ray crystallographic analyses of known S_2-receptor antagonists have shown that ketanserin,[18] metergoline,[19] pipanperon,[20] and haloperidol[21] have a common extended conformation, but spiperone, with the neuroleptics displaying dopamine-blocking activity and potent S_2-receptor-blocking activity as well, had the folded conformation.[22] A recent investigation by Azibi *et al.* showed the conformational flexibility of spiperone and confirmed the existence of extended and folded conformers in two polymorphs of spiperone by X-ray analysis.[23] The structure–activity relationships in our study indicate that the favorable structure interacting with S_2-receptors approximates the folded conformation proposed as the preferred form of spiperone.[24] A consideration of the folded conformation shown by the X-ray analysis of *cis*-17b (CV-5197) suggests that two aromatic rings, a 7-methoxy group, a 3-quasi-axial hydroxy group along with the oxygen atom in the skeleton and the essential nitrogen atom attached to the 4-propyl side chain are significant for the biological activity.

Further evaluation of CV-5197 revealed higher selectivity for the S_2 binding sites than the S_1 ones in the radioligand binding assay in rat brain synaptosomes and practically no inhibitory action on any other agonist, including histamine and acetylcholine.[25] The detailed pharmacological profiles of CV-5197 and its actions on circulatory disorders in experimental animal models will be described elsewhere.[26]

Experimental

All melting points were determined on a micro melting point apparatus (Yanagimoto) and are uncorrected. IR spectra were obtained with Hitachi 215 and 260-10 spectrophotometers. ^{1}H-NMR spectra were measured with Varian T-60, EM-390, and JEOL JNM-GX400 NMR spectrometers and the 60 MHz spectral data are given, unless otherwise mentioned. Mass spectra (MS) were taken on JEOL JMS-01SC and Hitachi M-80A (high-resolution MS)

TABLE VII. Physicochemical Properties of Methyl 4-Substituted 3-Oxo-3,4-dihydro-2H-1,5-benzoxathiepin-4-carboxylates (2—5)

Compd. No.	R_1	X	Yield (%)	mp (°C)	Formula	C	H	N
2b	7-OCH$_3$	(CH$_2$)$_3$Cl	44	64—65	C$_{15}$H$_{17}$ClO$_5$S	52.33 (52.25)	5.10 (4.97)	
2c	8-OCH$_3$	(CH$_2$)$_3$Cl	42	Oil	C$_{15}$H$_{17}$ClO$_5$S	52.33 (52.14)	5.10 (5.23)	
2d	7-Cl	(CH$_2$)$_3$Cl	32	Oil	C$_{14}$H$_{14}$Cl$_2$O$_4$S	48.15 (48.36)	4.04 (4.27)	
2e	7-CH$_3$	(CH$_2$)$_3$Cl	37	Oil	C$_{15}$H$_{17}$ClO$_4$S	54.79 (54.52)	5.21 (5.48)	
2f	7-OCH$_2$Ph	(CH$_2$)$_3$Cl	36	88—89	C$_{21}$H$_{21}$ClO$_5$S	59.93 (59.89)	5.03 (5.02)	
3b	7-OCH$_3$	(CH$_2$)$_4$Br	32	Oil	C$_{16}$H$_{19}$BrO$_5$S	47.65 (47.39)	4.75 (4.86)	
4b	7-OCH$_3$	(CH$_2$)$_5$Br	31	Oil	C$_{17}$H$_{21}$BrO$_5$S	48.92 (48.81)	5.07 (5.26)	
5b	7-OCH$_3$	CH$_2$CON⟩NPh	69	146—148	C$_{24}$H$_{26}$N$_2$O$_6$S	61.26 (61.40)	5.57 (5.60)	5.94 (5.90)

mass spectrometers. In the NMR spectra, chemical shifts are given in the δ (ppm) scale with tetramethylsilane as an internal standard.

Reactions were run at room temperature unless otherwise noted, and followed by TLC on Merck F-254 silicagel plates. Standard work-up procedures were as follows. The reaction mixture was partitioned between the indicated solvent and water. The organic extract was washed with water (H_2O). The extract was dried over anhydrous Na_2SO_4, filtered and concentrated under reduced pressure. Chromatographic separation was done on Merck Silica gel 60 with the indicated eluant.

Methyl 4-(ω-Halogenoalkyl)-3-oxo-3,4-dihydro-2H-1,5-benzoxathiepin-4-carboxylates (2—5, Table VII)——A typical example of the experimental procedure used to obtain 2—5 is as follows. A mixture of methyl 7-methoxy-3-oxo-3,4-dihydro-2H-1,5-benzoxathiepin-4-carboxylate (**1b**) (2.0 g, 7 mmol), 1-bromo-3-chloropropane (2.3 g, 15 mmol), K_2CO_3 (1.5 g, 11 mmol), KI (1.2 g, 7 mmol) and CH_3CN (30 ml) was refluxed with stirring under an N_2 stream for 3 h. After filtration of the reaction mixture, the filtrate was concentrated *in vacuo*. The residue was diluted with H_2O and worked up (AcOEt; H_2O). The residue was subjected to column chromatography on silica gel (hexane : CH_2Cl_2 : AcOEt = 30 : 15 : 1). Compound **2b** (1.12 g, 44%) was obtained from the first fraction as colorless prisms (recrystallized from EtOH). IR ν_{max}^{KBr} cm^{-1}: 1760, 1725, 1600, 1485, 1260, 1240, 1210, 1175, 1040. ^{1}H-NMR (CDCl$_3$) δ: 1.8—2.2 (4H, m), 3.57 (2H, t, $J = 6$ Hz, CH$_2$Cl), 3.73 (3H, s), 3.75 (3H, s), 4.47 (1H, d, $J = 18$ Hz, C$_2$-H), 4.73 (1H, d, $J = 18$ Hz, C$_2$-H), 6.55 (1H, dd, $J = 8$, 2 Hz, C$_8$-H), 6.57 (1H, d, $J = 2$ Hz, C$_6$-H), 6.88 (1H. d, $J = 8$ Hz, C$_9$-H).

The second fraction yielded methyl 3-(3-chloropropyloxy)-7-methoxy-2H-1,5-benzoxathiepin-4-carboxylate. (0.38 g, 15%) as a colorless oil. MS m/z: 344, 346 (M$^+$). IR ν_{max}^{neat} cm^{-1}: 1720 (ester). ^{1}H-NMR (CDCl$_3$) δ: 2.18 (2H, m), 3.70 (2H, t, $J = 6$ Hz, CH$_2$Cl), 3.72 (3H, s), 3.80 (3H, s), 4.10 (2H, t, $J = 6$ Hz, OCH$_2$CH$_2$), 5.10 (2H, s, C$_2$-H). Compounds 2—5 were prepared by similar alkylation of 1a—f with the corresponding ω-halogenoalkylbromides, and their physical data are listed in Table VII.
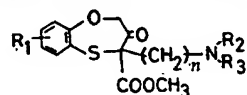
Methyl cis- and trans-3-Hydroxy-7-methoxy-4-[2-oxo-2-(4-phenyl-1-piperazinyl)ethyl]-3,4-dihydro-2H-1,5-ben-zoxathiepin-4-carboxylates (cis- and trans-6b)——NaBH$_4$ (0.38 g, 10 mmol) was added in small portions to a solution of 5b (3.1 g, 6.7 mmol) in MeOH (50 ml). The mixture was stirred for 1 h and then poured into ice-H$_2$O. The resulting precipitates were collected by filtration and recrystallized from AcOEt to give cis-6b (1.8 g, 57%) as colorless prisms, mp 213—215 °C. *Anal.* Calcd for C$_{24}$H$_{28}$N$_2$O$_6$S: C, 61.00; H, 5.97; N, 5.93. Found: C, 60.87; H, 5.84; N, 5.86. IR ν_{max}^{KBr} cm^{-1}: 3500 (OH), 1740 (ester), 1650 (amide). ^{1}H-NMR (400 MHz) (CDCl$_3$) δ: 3.907 (1H, dd, $J = 1.2$, 13.2 Hz, C$_2$-H), 4.128 (1H, dd, $J = 1.2$, 4.4 Hz, C$_3$-H), 4.341 (1H, dd, $J = 4.4$, 13.2 Hz, C$_2$-H). Chromatographic purification of the mother liquor gave trans-6b (0.4 g, 13%) as a colorless oil, which was converted into the hydrochloride, colorless crystals, mp 170—180 °C (dec.). *Anal.* Calcd for C$_{24}$H$_{28}$N$_2$O$_6$S·HCl·1/2H$_2$O: C, 55.64; H, 5.83; N, 5.40. Found: C, 55.38; H, 5.73; N, 5.44. IR ν_{max}^{KBr} cm^{-1}: 3550, 1740, 1650. ^{1}H-NMR(400 MHz) (DMSO-d_6) δ: 4.082 (1H, dd, $J = 5.7$, 12.6 Hz, C$_2$-H), 4.185 (1H, ddd, $J = 2.2$, 5.7, 7.3 Hz, C$_3$-H), 4.300 (1H, dd, $J = 2.2$, 12.6 Hz, C$_2$-H), 5.546 (1H, d, $J = 7.3$ Hz, OH).

Methyl 4-Aminoalkyl-Substituted 3-Oxo-3,4-dihydro-2H-1,5-benzoxathiepin-4-carboxylates (7—14, Table VIII)——A typical example of the experimental procedure used to obtain 7—14 is as follows. Method A) A mixture of 2b (56 g, 0.16 mol), N-phenylpiperazine (40 g, 0.26 mol), K$_2$CO$_3$ (34 g, 0.25 mol), KI (5.5 g, 33 mmol) and DMF (250 ml) was stirred at 70 °C for 7 h. The reaction mixture was poured into ice-H$_2$O and extracted with AcOEt. The organic layer was worked up and the residue was recrystallized from MeOH to give 7b (57 g, 75%) as colorless crystals. IR ν_{max}^{KBr} cm^{-1}: 1755 (ester), 1720 (CO), 1600, 1485, 1265, 1240, 1225, 1205, 1045. ^{1}H-NMR (CDCl$_3$) δ: 1.2—3.3 (14H, m), 3.68 (3H, s), 3.72 (3H, s), 4.38 (1H, d, $J = 18$ Hz, C$_2$-H), 4.72 (1H, d, $J = 18$ Hz, C$_2$-H), 6.4—7.4 (8H, m). Method B) A mixture of 1b (5 g, 19 mmol), 3-(4-phenyl-1-piperazinyl)propyl chloride (6.7 g, 28 mmol), K$_2$CO$_3$ (4.65 g, 34 mmol), KI (3 g, 18 mmol) and CH$_3$CN (150 ml) was refluxed with stirring for 4 h. The reaction mixture was filtered and the filtrate was concentrated *in vacuo*. The residue was diluted with H$_2$O and extracted with AcOEt. The organic layer was worked up and the residue was purified by column chromatography on silica gel (hexane : AcOEt = 2 : 1) to give 7b (2.7 g, 31%) as colorless crystals. Compounds 7—14 were similarly prepared by the substitution of 2—4 with the corresponding amines (method A) or by the alkylation of 1 with 3-(4-phenyl-1-piperazinyl)propyl chloride (method B), and their physical data are listed in Table VIII.

Methyl cis- and trans-4-(3-Chloropropyl)-3-hydroxy-7-methoxy-3,4-dihydro-2H-1,5-benzoxathiepin-4-carboxyl-ates (cis- and trans-15b)——NaBH$_4$ (0.3 g, 8 mmol) was added in small portions to an ice-cooled solution of 2b (2.0 g, 6 mmol) in MeOH (15 ml) and THF (8 ml) with stirring. The mixture was stirred for 1 h, then poured into ice-H$_2$O and worked up (AcOEt; H$_2$O). The residue was subjeced to column chromatography on silica gel (hexane : AcOEt = 2 : 1) to give trans-15b (0.5 g, 25%) from the first fraction, as colorless needles, mp 108—110 °C (recrystallized from AcOEt-hexane). *Anal.* Calcd for C$_{15}$H$_{19}$ClO$_5$S: C, 51.95; H, 5.52. Found: C, 51.63; H, 5.51. IR ν_{max}^{KBr} cm^{-1}: 3500 (OH), 1730 (ester). ^{1}H-NMR (CDCl$_3$) δ: 1.95 (4H, m, CH$_2$CH$_2$CH$_2$Cl), 3.48 (2H, t, $J = 6.5$ Hz, CH$_2$Cl), 3.58 (3H, s), 3.70 (3H, s), 4.0—4.2 (3H, m).

The second fraction yielded cis-15b (1.25 g, 63%) as colorless prisms, mp 80—82 °C (recrystallized from EtOH). *Anal.* Calcd for C$_{15}$H$_{19}$ClO$_5$S: C, 51.95; H, 5.52. Found: C, 51.61; H, 5.48. IR ν_{max}^{KBr} cm^{-1}: 3540 (OH), 1735 (ester), 1600, 1485, 1440, 1250, 1210. ^{1}H-NMR (CDCl$_3$) δ: 1.4—2.4 (4H, m), 3.40 (2H, t, $J = 4$ Hz, CH$_2$Cl), 3.75 (3H, s), 3.80

TABLE VIII. Physicochemical Properties of Methyl 4-Aminoalkyl-Substituted 3-Oxo-3,4-dihydro-2H-1,5-benzoxathiepin-4-carboxylates (7—14)

Compd. No.	R_1	n	$N{<}^{R_2}_{R_3}$	Meth-od	Yield (%)	mp (°C)	Formula	C	H	N
7a	H	3	N◯N-Ph	B	18	176—178	$C_{24}H_{28}N_2O_4S \cdot$ HCl·1/2H$_2$O	59.67 (59.49	6.26 6.33	5.83 5.79)
7b	7-OCH$_3$	3	N◯N-Ph	A B	75 31	110—112	$C_{25}H_{30}N_2O_3S$	63.81 (63.50	6.43 6.37	5.95 5.71)
7c	8-OCH$_3$	3	N◯N-Ph	B	32	140—145	$C_{25}H_{30}N_2O_3S\cdot$ 2HCl·H$_2$O	53.47 (53.55	6.10 5.87	4.99 5.00)
7d	7-Cl	3	N◯N-Ph	A B	76 27	197—199	$C_{24}H_{27}ClN_2O_4S\cdot$ 2HCl·1/2H$_2$O	51.76 (52.02	5.43 5.12	5.03 5.08)
7e	7-CH$_3$	3	N◯N-Ph	A B	78 29	145—150	$C_{25}H_{30}N_2O_4S\cdot$ 2HCl·1/2H$_2$O	55.96 (56.11	6.20 6.19	5.22 5.11)
8b	7-OCH$_3$	3	N◯N-◯Cl	A	73	153—156	$C_{25}H_{29}N_2O_5S\cdot$ 2HCl	51.95 (51.85	5.41 5.42	4.85 4.74)
9b	7-OCH$_3$	3	N◯N-◯OCH$_3$	A	75	185—190	$C_{26}H_{32}N_2O_6S\cdot$ 2HCl	54.45 (54.46	5.98 5.94	4.89 4.83)
10b	7-OCH$_3$	3	N◯N-◯-OCH$_3$	A	76	133—135	$C_{26}H_{32}N_2O_5S\cdot$ 1/2H$_2$O	61.27 (60.95	6.26 6.30	5.50 5.48)
11b	7-OCH$_3$	3	N◯N-CH⟨Ph,Ph⟩	A	62	152—155	$C_{32}H_{36}N_2O_5S\cdot$ 2HCl·2$^1/_2$H$_2$O	56.63 (56.64	6.39 6.16	4.13 4.15)
12b	7-OCH$_3$	3	N◯N-◯N	A	58	158—162	$C_{24}H_{29}N_3O_5S\cdot$ 2HCl·1$^1/_2$H$_2$O	50.44 (50.69	5.99 5.81	7.35 7.30)
13b	7-OCH$_3$	4	N◯N-Ph	A B	49 22	155—165	$C_{26}H_{32}N_2O_5S\cdot$ 2HCl·1/2H$_2$O	55.12 (55.30	6.22 6.19	4.95 4.96)
14b	7-OCH$_3$	5	N◯N-Ph	A B	44 18	130—150	$C_{27}H_{34}N_2O_5S\cdot$ 2HCl·1/2H$_2$O	55.85 (56.00	6.42 6.41	4.83 4.81)

(3H, s), 3.7—4.4 (3H, m), 6.80 (1H, dd, $J=2, 4$ Hz, C$_7$-H), 6.9—7.1 (2H, m). Similar NaBH$_4$ reduction of 2f gave cis- and trans-15f, respectively.

Methyl cis-7-Benzyloxy-4-(3-chloropropyl)-3-hydroxy-3,4-dihydro-2H-1,5-benzoxathiepin-4-carboxylate (cis-15f)——Yield 50%. Colorless oil. Anal. Calcd for $C_{21}H_{23}ClO_5S$: C, 59.64; H, 5.48. Found: C, 59.77; H, 5.39.

Methyl trans-7-Benzyloxy-4-(3-chloropropyl)-3-hydroxy-3,4-dihydro-2H-1,5-benzoxathiepin-4-carboxylate (trans-15f)——Yield 30%. Colorless prisms, mp 97—99°C (recrystallized from AcOEt-hexane). Anal. Calcd for $C_{21}H_{23}ClO_5S$: C, 59.64; H, 5.48. Found: C, 59.80; H, 5.51.

Methyl cis-3-Hydroxy-7-methoxy-4-[2-(4-phenyl-1-piperazinyl)ethyl]-3,4-dihydro-2H-1,5-benzoxathiepin-4-car-boxylate (cis-16b)——AcOH (0.48 g, 8 mmol), was added to a suspension of NaBH$_4$ (0.30 g, 8 mmol) in THF (20 ml). The mixture was gently boiled for 0.5 h, and then cis-6b (0.5 g, 7 mmol) was added to the above mixture. The mixture was refluxed for 20 h. The reaction mixture was worked up (AcOEt; H$_2$O) and the residue was purified by column chromatography on silica gel (hexane:AcOEt=1:1) to give cis-16b (0.20 g, 42%) as a colorless oil, which was converted into the hydrochloride, cis-16b·2HCl, colorless crystals (from MeOH). IR ν_{max}^{KBr} cm^{-1}: 3520, 1740 (ester). ^{1}H-NMR (400 MHz) (DMSO-d_6-D$_2$O) δ: 4.022 (1H, dd, $J=2.7, 12.7$ Hz, C$_2$-H), 4.080 (1H, dd, $J=2.7, 6.1$ Hz, C$_3$-H), 4.168 (1H, dd, $J=6.1, 12.7$ Hz, C$_2$-H).

Methyl 4-Aminoalkyl-Substituted 3-Hydroxy-3,4-dihydro-2H-1,5-benzoxathiepin-4-carboxylates (17—36, Table I)——Method C) NaBH$_4$ (0.51 g, 13.5 mmol) was added in small portions to an ice-cooled solution of 7b (12.6 g, 27 mmol) in MeOH (100 ml) and THF (30 ml) with stirring. The mixture was stirred for 3 h. The reaction mixture was poured into ice-H$_2$O and extracted with AcOEt. The organic layer was worked up. The residue obtained was subjected to column chromatography on silica gel (hexane:AcOEt=2:1—1:3). trans-17b was obtained from the

first fraction as a pale yellow oil, which was isolated as the hydrochloride, *trans*-17b·HCl (4.6 g), colorless prisms (recrystallized from 50% EtOH). IR v_{max}^{KBr} cm^{-1}: 3530, 3500—3200, 2700—2300, 1720, 1600, 1485, 1255, 1235, 1205, 1035. ^{1}H-NMR (400 MHz) (DMSO-d_6–D$_2$O) δ: 3.667 (3H, s), 3.746 (3H, s), 3.794 (1H, dd, J=8.4, 12.7 Hz, C$_2$-H), 4.107 (1H, dd, J=3.8, 12.7 Hz, C$_2$-H), 4.383 (1H, dd, J=3.8, 8.4 Hz, C$_3$-H).

The second fraction yielded *cis*-17b as a colorless oil, which was converted into the hydrochloride, *cis*-17b·HCl (6.9 g), colorless prisms (recrystallized from 50% EtOH). IR v_{max}^{KBr} cm^{-1}: 3600—3300, 1735, 1720, 1595, 1480, 1250. ^{1}H-NMR (400 MHz) (DMSO-d_6–D$_2$O) δ: 3.693 (3H, s), 3.758 (3H, s), 3.873 (1H, dd, J=0—1, 13.1 Hz, C$_2$-H), 3.999 (1H, dd, J=0—1, 4.6 Hz, C$_3$-H), 4.155 (1H, dd, J=4.6, 13.1 Hz, C$_2$-H). Method D) A mixture of *cis*-15b (95 g, 0.20 mol), *N*-phenylpiperazine (50 g, 0.33 mol), K$_2$CO$_3$ (42 g, 0.31 mol) and DMF (400 ml) was stirred at 70 °C for 8 h. The reaction mixture was worked up (AcOEt; H$_2$O). The residue was purified by column chromatography on silica gel (hexane : AcOEt = 2 : 3) to give *cis*-17b, which was isolated as the hydrochloride (83.7 g, 56%).

Compounds 17—36 were similarly prepared by method C or method D, and their physicochemical properties are listed in Table I.

Methyl .cis-3,7-Dihydroxy-4-[3-(4-phenyl-1-piperazinyl)propyl]-3,4-dihydro-2H-1,5-benzoxathiepin-4-carboxylate (*cis*-17 g, Table I)——Method E) Pd black (1.0 g) was added to a solution of *cis*-17f (2.45 g), conc. HCl (1.1 ml), and MeOH (200 ml). The mixture was hydrogenated under atmospheric pressure of H$_2$ for 20 h. After filtration of the catalyst, the filtrate was concentrated *in vacuo*. The residue was purified by column chromatography on silica gel (hexane : AcOEt : MeOH = 30 : 30 : 1), followed by recrystallization from·AcOEt to give *cis*-17g (1.31 g, 64%) as colorless crystals. IR v_{max}^{KBr} cm^{-1}: 3450 (OH), 1730 (ester). ^{1}H-NMR (CDCl$_3$) δ: 1.1—3.4 (14H, m), 3.72 (3H, s, COOCH$_3$). 4.0—4.1 (3H, m), 6.6—7.4 (8H, m). MS *m/z*: 458 (M$^+$).

Similarly, catalytic hydrogenation of *cis*-36f and *cis*-37f gave *cis*-38g and *cis*-39g (Table I), respectively.

Methyl *cis*-7-Benzyloxy-3-hydroxy-4-(3-piperazinylpropyl)-3,4-dihydro-2H-1,5-benzoxathiepin-4-carboxylate (*cis*-37f, Table I)——A mixture of *cis*-15f (2.0 g, 4.7 mmol), *N-tert*-butyloxycarbonylpiperazine (1.76 g, 9.5 mmol), K$_2$CO$_3$ (0.98 g, 7 mmol), KI (0.4 g, 2.4 mmol) and CH$_3$CN (20 ml) was refluxed for 6 h. The reaction mixture was worked up (AcOEt; H$_2$O) and the residue was purified by column chromatography on silica gel (hexane : AcOEt = 3 : 2) to give the *tert*-butyloxycarbonyl derivative of *cis*-37f (1.8 g, 69%) as a colorless oil. MS *m/z*: 572 (M$^+$), which was treated with HCl–AcOEt to give *cis*-37f (1.6 g) as colorless prisms (recrystallized from MeOH). IR v_{max}^{KBr} cm^{-1}: 3400 (OH), 1730 (ester). ^{1}H-NMR (DMSO-d_6) δ: 1.2—2.4 (6H, m), 3.40—3.60 (8H, m), 3.68 (3H, s, COOCH$_3$), 3.9—4.1 (3H, m), 5.16 (2H, s, CH$_2$Ph), 6.7—7.5 (8H, m).

Methyl *cis*- and *trans*-3-(3-Hydroxy-7-methoxy-3,4-dihydro)2H-1,5-benzoxathiepin-2-yl)propionate (*cis*- and *trans*-41b)——NaBH$_4$ (0.2 g, 5.3 mmol) was added in small portions to a solution of 40b$^{1)}$ (2.0 g, 6.7 mmol) in MeOH (20 ml) and THF (20 ml) with stirring. The mixture was stirred for 3 h. The reaction mixture was poured into ice-H$_2$O and extracted with AcOEt. The organic layer was worked up. The residue was subjected to column chromatography on silica gel (hexane : CH$_2$Cl$_2$: AcOEt = 3 : 3 : 1) to give *cis*-41b (0.94 g, 47%) from the first fraction, as colorless crystals, mp 88—89 °C (recrystallized from Et$_2$O-petroleum ether). *Anal.* Calcd for C$_{14}$H$_{18}$O$_5$S: C, 56.36; H, 6.08. Found: C, 56.50; H, 6.04. IR v_{max}^{KBr} cm^{-1}: 3490 (OH), 1730 (ester). ^{1}H-NMR (400 MHz) (CDCl$_3$) δ: 2.950 (1H, dd, J=2.0, 14.3 Hz, C$_4$-H), 3.000 (1H, dd, J=5.0, 14.3 Hz, C$_4$-H), 3.574 (1H, ddd, J=0—1, 3.3, 10.4 Hz, C$_2$-H), 3.966 (1H, ddd, J=0—1, 2.0, 5.0 Hz, C$_3$-H).

From the second fraction, *trans*-41b (0.72 g, 36%) was obtained as colorless crystals, mp 65—66 °C (recrystallized from Et$_2$O-petroleum ether). *Anal.* Calcd for C$_{14}$H$_{18}$O$_5$S: C, 56.36; H, 6.08. Found: C, 56.48; H, 6.10. IR v_{max}^{KBr} cm^{-1}: 3450 (OH). 1725 (ester). ^{1}H-NMR (400 MHz) (CDCl$_3$) δ: 2.739 (1H, dd, J=4.6, 14.6 Hz, C$_4$-H), 3.558 (1H, dd, J=2.6, 14.6 Hz, C$_4$-H), 3.910 (1H, ddd, J=2.4, 6.0, 8.0 Hz, C$_2$-H), 3.950 (1H, ddd, J=2.6, 4.6, 8.0 Hz, C$_3$-H).

Methyl *cis*-(3-Hydroxy-8-methoxy-3,4-dihydro-2H-1,5-benzoxathiepin-2-yl)propionate (*cis*-41c)——NaBH$_4$ reduction of 40c as described for 40b gave *cis*-41c (86% yield) as a colorless oil. *Anal.* Calcd for C$_{14}$H$_{18}$O$_5$S: C, 56.36; H, 6.08. Found: C, 56.55; H, 6.19. IR v_{max}^{neat} cm^{-1}: 3480 (OH), 1730 (ester).

cis-7-Methoxy-2-[3-oxo-3-(4-phenyl-1-piperazinyl)propyl]-3,4-dihydro-2H-1,5-benzoxathiepin-3-ol (*cis*-42b)—— A mixture of *cis*-41b (300 mg, 1 mmol) and *N*-phenylpiperazine (1 ml) was stirred at 90 °C for 3 h. The reaction mixture was worked up (AcOEt; H$_2$O). The residue was recrystallized from AcOEt-Et$_2$O to yield *cis*-42b (320 mg, 74%) as colorless crystals, mp 110—111 °C. *Anal.* Calcd for C$_{23}$H$_{28}$N$_2$O$_4$S: C, 64.46; H, 6.59; N, 6.54. Found: C, 64.62; H, 6.51; N, 6.52. IR v_{max}^{KBr} cm^{-1}: 3400 (OH), 1645 (amide).

Similar amidation of *trans*-41b and *cis*-41c gave *trans*-42b and *cis*-42c, respectively.

trans-7-Methoxy-2-[3-oxo-3-(4-phenyl-1-piperazinyl)propyl]-3,4-dihydro-2H-1,5-benzoxathiepin-3-ol (*trans*-42b) ——Yield 75%. Recrystallization from AcOEt gave colorless crystals, mp 139—140 °C. *Anal.* Calcd for C$_{23}$H$_{28}$N$_2$O$_4$-S: C, 64.46; H, 6.59; N, 6.54. Found: C, 64.52; H, 6.31; N,.6.61.

cis-8-Methoxy-2-[3-oxo-3-(4-phenyl-1-piperazinyl)propyl]-3,4-dihydro-2H-1,5-benzoxathiepin-3-ol (*cis*-42c)—— Yield 71%. Colorless prisms, mp 126—127 °C (recrystallized from AcOEt). *Anal.* Calcd for C$_{23}$H$_{28}$N$_2$O$_4$S: C, 64.46; H, 6.31; N, 6.61. Found: C, 64.30; H, 6.60; N, 6.43.

cis-7-Methoxy-2-[3-(4-phenyl-1-piperazinyl)propyl]-3,4-dihydro-2H-1,5-benzoxathiepin-3-ol (*cis*-43b)——A solution of *cis*-42b (350 mg, 0.8 mmol) in THF (10 ml) was added dropwise to a suspension of LiAlH$_4$ (100 mg, 2.6 mmol)

in dry Et_2O (20 ml) with stirring under an atmosphere of dry N_2. The mixture was refluxed for 3 h. The reaction mixture was diluted with 20% NaOH and filtered off. The filtrate was concentrated *in vacuo*. The residue was purified by column chromatography on silica gel (hexane:AcOEt:MeOH = 10:10:1) to give *cis*-43b (270 mg, 80%) as colorless crystals, mp 107—109 °C (recrystallized from AcOEt). *Anal*. Calcd for $C_{23}H_{30}N_2O_3S$: C, 66.64; H, 7.29; N, 6.76. Found: C, 66.59; H, 7.22; N, 6.90. IR ν_{max}^{KBr} cm^{-1}: 3450—3300 (OH), 1585, 1475, 1230, 1030, 915. ^{1}H-NMR (400 MHz) (CDCl$_3$) δ: 2.953 (1H, dd, J=2.1, 14.2 Hz, C$_4$-H), 3.039 (1H, dd, J=5.4, 14.2 Hz, C$_4$-H), 3.609 (1H, ddd, J=0—1, 4.0, 9.6 Hz, C$_2$-H), 3.975 (1H, ddd, J=0—1, 2.1, 5.4 Hz, C$_3$-H).

Similar LiAlH$_4$ reduction of *trans*-42b and *cis*-42c gave *trans*-43b and *cis*-43c, respectively.

trans-7-Methoxy-2-[3-(4-phenyl-1-piperazinyl)propyl]-3,4-dihydro-2H-1,5-benzoxathiepin-3-ol (*trans*-43b)——— Yield 77%. Recrystallization from AcOEt gave colorless crystals, mp 128—130 °C. *Anal*. Calcd for $C_{23}H_{30}N_2O_3S$: C, 66.64; H, 7.29; N, 6.76. Found: C, 66.50; H, 6.94; N, 6.56. IR ν_{max}^{KBr} cm^{-1}: 3450—3000 (OH), 1585, 1490, 1235, 1035. ^{1}H-NMR (400 MHz) (CDCl$_3$) δ: 2.735 (1H, dd, J=4.8, 14.5 Hz, C$_4$-H), 3.534 (1H, dd, J=2.3, 14.5 Hz, C$_4$-H), 3.96 (2H, m, C$_2$-H, C$_3$-H).

cis-8-Methoxy-2-[3-(4-phenyl-1-piperazinyl)propyl]-3,4-dihydro-2H-1,5-benzoxathiepin-3-ol (*cis*-43c)——Yield 76%. Recrystallization from AcOEt gave colorless prisms, mp 149—150 °C. *Anal*. Calcd for $C_{23}H_{30}N_2O_3S$: C, 66.64; H, 7.29; N, 6.76. Found: C, 66.71; H, 7.26; N, 6.79. IR ν_{max}^{KBr} cm^{-1}: 3400—3200 (OH), 1595, 1475, 1290, 1240, 1160, 1005. ^{1}H-NMR (400 MHz) (CDCl$_3$) δ: 2.886 (1H, dd, J=2.1, 14.2 Hz, C$_4$-H), 2.966 (1H, dd, J=5.4, 14.2 Hz, C$_4$-H), 3.668 (1H, ddd, J=0—1, 4.0, 9.4 Hz, C$_2$-H), 3.970 (1H, dd, J=0—1, 2.1, 5.4 Hz, C$_3$-H).

3-[2-(1,3-Dioxolan-2-yl)ethyl]-7-methoxy-3,4-dihydro-2H-1,5-benzoxathiepin-3-ol (45)——A solution of 44[1] (2.0 g, 9.5 mmol) in THF (10 ml) was added dropwise to a solution of Grignard reagent prepared from Mg (350 mg, 14 mmol), 2-(1,3-dioxolan-2-yl)ethyl bromide (2.6 g, 14 mmol) and THF (30 ml) with stirring. The mixture was stirred for 1 h. The reaction mixture was diluted with 1 N NaOH (20 ml) and worked up (AcOEt; H$_2$O). The residue was purified by column chromatography on silica gel (CH$_2$Cl$_2$:Et$_2$O=5:1) to give 45 (2.44 g, 82%) as a colorless oil. *Anal*. Calcd for $C_{15}H_{20}O_5S$: 57.67; H, 6.45. Found: C, 57.41; H, 6.52. IR ν_{max}^{neat} cm^{-1}: 3230 (OH), 1595, 1490, 1475, 1195. ^{1}H-NMR (90 MHz) (CDCl$_3$) δ: 1.6—1.8 (4H, m), 2.83 (2H, s, C$_4$-H), 3.75 (3H, s, OCH$_3$), 3.6—4.2 (6H, m), 5.93 (1H, t, J=3 Hz, CH$\langle^O_O$). MS m/z: 312 (M$^+$).

7-Methoxy-3-[3-(4-phenyl-1-piperazinyl)propyl]-3,4-dihydro-2H-1,5-benzoxathiepin-3-ol (46)——A 50% H$_2$SO$_4$ solution (2 ml) was added to a solution of 45 (2.9 g, 9.3 mmol) in acetone (20 ml) and H$_2$O (10 ml). The mixture was stirred for 3 h. The reaction mixture was concentrated to *ca*. 10 ml *in vacuo* and extracted with CH$_2$Cl$_2$. The organic layer was worked up and the residue was dissolved in CH$_3$CN (20 ml). N-Phenylpiperazine (1.6 g, 10 mmol) was added to the above solution, the mixture was stirred for 10 h, and then NaBH$_3$CN (130 mg, 20 mmol) and MeOH were added. The reaction mixture was stirred for 3 h, then diluted with 3 N HCl (10 ml) and stirred for 2 h. The mixture was washed with AcOEt. The aqueous layer was made alkaline with 3 N NaOH (20 ml) and extracted with AcOEt. The organic layer was worked up and the residue was purified by column chromatography on silica gel (hexane:AcOEt:MeOH = 10:10:1) to give 46 as a colorless oil, which was converted into the hydrochloride, 46·HCl (2.4 g, 57%), colorless plates, mp 216—219 °C (recrystallized from 50% EtOH). *Anal*. Calcd for $C_{23}H_{30}N_2O_3S$·HCl: C, 61.25; H, 6.93; N, 6.21. Found: C, 61.43; H, 6.70; N, 6.27. IR ν_{max}^{KBr} cm^{-1}: 3500—3200 (OH), 1595, 1485. ^{1}H-NMR (90 MHz) (DMSO-d_6) δ: 1.6—2.1 (4H, m), 2.90 (2H, s, C$_4$-H), 3.2—4.0 (10H, m), 3.67 (3H, s, OCH$_3$), 3.93 (2H, s, C$_2$-H).

4-(3-Chloropropyl)-7-methoxy-3,4-dihydro-2H-1,5-benzoxathiepin-3-one (47b)——A mixture of 2b (5.0 g, 14.5 mmol), LiCl (1.5 g, 35 mmol), H$_2$O (0.3 ml) and DMSO (30 ml) was stirred at 100 °C for 5 h. The reaction mixture was poured into ice-H$_2$O and extracted with AcOEt. The organic layer was washed with H$_2$O, dried and concentrated *in vacuo*. The residue was purified by column chromatography on silica gel (hexane:AcOEt=2:1) to give 47b (2.0 g, 48%) as a colorless oil. *Anal*. Calcd for $C_{13}H_{15}ClO_3S$: C, 54.45; H, 5.27. Found: C, 54.90; H, 5.24. IR ν_{max}^{neat} cm^{-1}: 1730, 1595, 1490, 1205. ^{1}H-NMR (CDCl$_3$) δ: 1.7—2.4 (4H, m), 3.4—4.0 (3H, m), 3.68 (3H, s, OCH$_3$), 4.43 (1H, d, J=17 Hz, C$_2$-H), 4.75 (1H, d, J=17 Hz, C$_2$-H).

cis-4-(3-Chloropropyl)-7-methoxy-3,4-dihydro-2H-1,5-benzoxathiepin-3-ol (*cis*-48b)——NaBH$_4$ reduction of 47b in MeOH and THF (5:1) and usual work up gave *cis*-48b (84% yield) as a colorless oil. *Anal*. Calcd for $C_{13}H_{17}ClO_3S$: C, 54.07; H, 5.93. Found: C, 54.46; H, 6.11. IR ν_{max}^{neat} cm^{-1}: 3450 (OH), 1580, 1485. ^{1}H-NMR (400 MHz) (CDCl$_3$) δ: 3.044 (1H, ddd, J=1.2, 5.6, 8.8 Hz, C$_4$-H), 3.659 (1H, dd, J=0.7, 12.5 Hz, C$_2$-H), 3.903 (1H, ddd, J=0.7, 1.2, 4.0 Hz, C$_3$-H), 4.367 (1H, dd, J=4.0, 12.5 Hz, C$_2$-H).

7-Methoxy-4-[3-(4-phenyl-1-piperazinyl)propyl]-3,4-dihydro-2H-1,5-benzoxathiepin-3-one (49b)——A mixture of 47b (1.8 g) and N-phenylpiperazine (2.4 g) was heated at 100 °C for 1 h. The reaction mixture was worked up (AcOEt; H$_2$O). The residue was purified by column chromatography on silica gel (hexane:AcOEt = 1:1) to give 49b (1.68 g, 65%) as a colorless oil. *Anal*. Calcd for $C_{23}H_{28}N_2O_3S$: C, 66.97; H, 6.84; N, 6.79. Found: C, 66.62; H, 6.73; N, 6.68. IR ν_{max}^{neat} cm^{-1}: 1725 (CO), 1595. ^{1}H-NMR (CDCl$_3$) δ: 1.5—2.0 (4H, m), 2.3—2.8 (4H, m), 3.65 (3H, s, OCH$_3$), 4.42 (1H, d, J=8 Hz, C$_4$-H), 4.73 (1H, d, J=18 Hz, C$_2$-H), 4.80 (1H, d, J=18 Hz, C$_2$-H).

cis-7-Methoxy-4-[3-(4-phenyl-1-piperazinyl)propyl]-3,4-dihydro-2H-1,5-benzoxathiepin-3-ol (*cis*-50b)——a) Substitution reaction of *cis*-48b with N-phenylpiperazine, as described for *cis*-17b (method D), gave *cis*-50b (42% yield) as

colorless prisms, mp 112—113 °C (recrystallized from AcOEt). *Anal.* Calcd for $C_{23}H_{30}N_2O_3S$: C, 66.64; H, 7.29; N, 6.76. Found: C, 66.95; H, 7.34; N, 6.92. IR ν_{max}^{KBr} cm^{-1}: 3500—3000, 1595, 1490, 1440, 1200, 1035. ^{1}H-NMR (400 MHz) (DMSO-d_6-D$_2$O) δ: 3.206 (1H, ddd, $J=3.8$, 4.6, 8.1 Hz, C$_4$-H), 3.776 (1H, dd, $J=8.5$, 12.2 Hz, C$_2$-H), 4.017 (1H, dd, $J=3.8$, 12.2 Hz, C$_2$-H), 4.152 (1H, dt, $J=3.8$, 8.5 Hz, C$_3$-H).

b) NaBH$_4$ reduction of **49b** in a solution of THF and MeOH (10:1) gave cis-**50b** (93% yield). The structure of cis-**50b** was determined by X-ray crystallographic analysis (Fig. 1).

cis-4-(3-Chloropropyl)-3-hydroxy-7-methoxy-3,4-dihydro-2*H*-1,5-benzoxathiepin-4-carboxylic Acid (*cis*-51b)——A 1 N NaOH solution (8 ml, 8 mmol) was added to a solution of cis-**16b** (2.0 g, 5.8 mmol) in MeOH (20 ml). The mixture was stirred for 14 h, then poured into ice-H$_2$O containing conc. HCl (5 ml). The resulting precipitates were collected by filtration and recrystallized from AcOEt to give cis-**51b** (1.25 g, 75%) as colorless prisms, mp 174—176 °C. *Anal.* Calcd for $C_{14}H_{17}ClO_5S$: C, 50.53; H, 5.15. Found: C, 50.60; H, 5.12. IR ν_{max}^{KBr} cm^{-1}: 3430, 1740, 1485, 1205, 1035. ^{1}H-NMR (DMSO-d_6) δ: 1.2—2.3 (4H, m), 3.43 (2H, t, $J=4$ Hz, CH$_2$Cl), 3.75 (3H, s, OCH$_3$), 3.7—4.4 (3H, m).

trans-4-(3-Chloropropyl)-7-methoxy-3,4-dihydro-2*H*-1,5-benzoxathiepin-3-ol (*trans*-48b)——cis-**51b** (700 mg) was heated at 180 °C for 0.5 h under atmosphere of dry N$_2$. After cooling, the residue was subjected to column chromatography on silica gel (hexane : CH$_2$Cl$_2$: AcOEt = 3 : 3 : 1) to give trans-**48b** (101 mg, 16%) as a colorless oil. *Anal.* Calcd for $C_{13}H_{17}ClO_3S$: C, 54.07; H, 5.93. Found: C, 54.33; H, 6.06. IR ν_{max}^{neat} cm^{-1}: 3450 (OH), 1600, 1485, 1200, 1035.

trans-7-Methoxy-4-[3-(4-phenyl-1-piperazinyl)propyl]-3,4-dihydro-2*H*-1,5-benzoxathiepin-3-ol (*trans*-50b)——A mixture of trans-**48b** (100 mg) and *N*-phenylpiperazine (200 mg) was heated at 90 °C for 2 h. The reaction mixture was subjected to column chromatography on silica gel (hexane : AcOEt : MeOH = 10:10:1) to give trans-**50b** as a colorless oil, which was converted into the hydrochloride, trans-**50b**·2HCl (50 mg, 29%), amorphous powder. *Anal.* Calcd for $C_{23}H_{28}N_2O_3S \cdot 2HCl \cdot H_2O$: C, 56.42; H, 6.85; N, 5.51. Found: C, 56.32; H, 6.75; N, 5.44. IR ν_{max}^{KBr} cm^{-1}: 3400, 2800—2200, 1595, 1490, 1440, 1200, 1035. ^{1}H-NMR (400 MHz) (DMSO-d_6-D$_2$O) δ: 3.031 (1H, ddd, $J=3.4$, 7.7, 9.3 Hz, C$_4$-H), 3.785 (1H, ddd, $J=2.7$, 4.9 7.7 Hz, C$_3$-H), 3.855 (1H, dd, $J=5.0$, 12.6 Hz, C$_2$-H), 4.329 (1H, dd, $J=2.8$, 12.6 Hz, C$_2$-H).

Methyl 5-(4-Phenyl-1-piperazinyl)-2-(6-methoxy-1,4-benzoxathian-3-yl)pentanoates (52 and 53)——a) A mixture of TsCl (3.0 g, 16 mmol) in pyridine (3 ml) was added dropwise to an ice-cooled solution of cis-**17b** (5.0 g, 11 mmol) in pyridine (15 ml). The mixture was stirred at 0—5 °C for 6 h and then poured into ice-H$_2$O. The supernatant was removed by decantation and the residue was worked up (AcOEt; H$_2$O). The residue was subjected to column chromatography on silica gel (hexane : AcOEt = 1 : 1) to give a gummy residue [2.0 g, MS *m/z*: 454 (M$^+$)]. Catalytic hydrogenation of the product obtained (2.0 g) in AcOEt (20 ml) was carried out in the presence of 5% Pd–C (100 mg) under atmospheric pressure of H$_2$. After hydrogen absorption had ceased (100 ml), the catalyst was filtered off and the filtrate was concentrated *in vacuo*. The residue was subjected to column chromatography on silica gel (hexane : AcOEt : MeOH = 10 : 10 : 1) to give 52 from the first fraction as a colorless oil, which was converted into the hydrochloride, 52·HCl (360 mg, 7% from cis-**17b**), colorless prisms, mp 121—123 °C (recrystallized from 50% EtOH). *Anal.* Calcd for $C_{25}H_{32}N_2O_4S \cdot HCl \cdot H_2O$: C, 58.75; H, 6.90; N, 5.48. Found: C, 58.39; H, 6.79; N, 5.30. IR ν_{max}^{KBr} cm^{-1}: 3500. 3430, 2700—2300, 1730 (ester), 1595, 1485, 1260, 1205, 1195. ^{1}H-NMR (400 MHz) (DMSO-d_6-D$_2$O) δ: 2.730 (1H, ddd, $J=3.4$, 9.5, 10.0 Hz, -CHCOOCH$_3$), 3.612 (1H, ddd, $J=2.1$, 5.4, 9.5 Hz, C$_3$-H), 4.115 (1H, dd, $J=5.4$, 12.0 Hz, C$_2$-H), 4.263 (1H, dd, $J=2.1$, 12.0 Hz, C$_2$-H).

The second fraction gave 53 as a colorless oil, which was isolated as the hydrochloride 53·HCl (320 mg, 6% from cis-**17b**). Recrystallization from 50% EtOH gave colorless prisms, mp 152—154 °C. *Anal.* Calcd for $C_{25}H_{32}N_2O_4S \cdot HCl$: C, 60.90; H, 6.75; N, 5.68. Found: C, 60.53; H, 6.83; N, 5.70. IR ν_{max}^{KBr} cm^{-1}: 3520, 3450, 2700—2300, 1725, 1595, 1490, 1440, 1260, 1245, 1200. ^{1}H-NMR (400 MHz) (DMSO-d_6-D$_2$O) δ: 2.805 (1H, ddd, $J=3.4$, 9.8, 10.5 Hz, -CHCOOCH$_3$), 3.599 (1H, ddd, $J=2.0$, 4.2, 9.8 Hz, C$_3$-H), 4.184 (1H, dd, $J=2.0$, 12.2 Hz, C$_2$-H), 4.439 (1H, dd, $J=4.2$, 12.2 Hz, C$_2$-H).

b) A mixture of red P (300 mg, 10 mmol). I$_2$ (90 mg) and AcOH (6 ml) was stirred for 0.5 h. cis-**16b** (3.0 g, 8.7 mmol) and H$_2$O (0.1 ml) were added to the above mixture and the mixture was refluxed for 1 h. The reaction mixture was worked up (AcOEt; H$_2$O) and the residue was subjected to column chromatography on silica gel (hexane : AcOEt = 2 : 1) to give a colorless oil [1.38 g, MS *m/z*: 330, 332 (M$^+$)], which was heated with *N*-phenylpiperazine (4 ml) at 90 °C for 2 h. The mixture obtained was subjected to column chromatography on silica gel (hexane : AcOEt : MeOH = 10 : 10 : 1) to give first 52 (isolated as 52·HCl; 0.46 g, 11% from cis-**15b**) and then 53 (isolated as 53·HCl; 0.38 g, 9% from cis-**15b**).

1-Chloro-5-(1,3-dioxolan-2-yl)pentan-3-ol (54)——A solution of 3-chloropropanal (3.3 g, 36 mmol) in THF (10 ml) was added to a solution of 2-(1,3-dioxolan-2-yl)ethylmagnesium bromide prepared from Mg (1.0 g, 41 mmol), 2-(1,3-dioxolan-2-yl)ethyl bromide (7.5 g, 41 mmol) and THF (20 ml). The mixture was stirred for 2 h, then diluted with 1 N NaOH (20 ml) and worked up (AcOEt; H$_2$O). The residue was purified by column chromatography on silica gel (CH$_2$Cl$_2$: Et$_2$O = 5 : 1) to give 54 (2.6 g, 73%) as a colorless oil. *Anal.* Calcd for $C_8H_{15}ClO_3$: C, 49.36; H, 7.77. Found: C, 49.55; H, 7.51. IR ν_{max}^{neat} cm^{-1}: 3400 (OH), 1450, 1415, 1345, 1210, 1040. ^{1}H-NMR (CDCl$_3$) δ: 1.2—2.2 (6H, m), 3.4—4.2 (7H, m), 4.91 (1H, t, $J=4$ Hz, O-CH-O).

5-(1,3-Dioxolan-2-yl)-3-mesyloxypentyl Benzoate (55)——A mixture of **54** (3.0 g, 15 mmol), sodium benzoate (3.0 g, 21 mmol), KI (1.0 g, 6 mmol), CH_3CN (30 ml) and DMF (20 ml) was stirred at 80 °C for 5 h. The reaction mixture was worked up (AcOEt; H_2O) and the residue was purified by column chromatography on silica gel ($CH_2Cl_2 : Et_2O = 5 : 1$) to give 5-(1,3-dioxolan-2-yl)-3-hydroxypentyl benzoate (1.8 g, 42%) as a colorless oil [MS m/z: 280 (M⁺)]. MsCl (1.8 g, 6.4 mmol) was added to the alcohol obtained above (1.8 g) in pyridine (10 ml). The mixture was stirred for 2 h, poured into ice-H_2O containing conc. HCl (20 ml) and extracted with CH_2Cl_2. The organic layer was washed with H_2O, dried and concentrated *in vacuo*. The residue was purified by column chromatography on silica gel ($CH_2Cl_2 : Et_2O = 5 : 1$) to give **55** (0.9 g, 54%) as a colorless oil. MS m/z: 358 (M⁺), 357. High-resolution MS Calcd for $C_{16}H_{22}O_7S$: 358.1085. Found: 358.1088. IR ν_{max}^{neat} cm⁻¹: 1725, 1710, 1595, 1445, 1350, 1280, 1270, 1175. ¹H-NMR ($CDCl_3$) δ: 1.7—2.4 (6H, m), 3.08(3H, s, OSO_2CH_3), 3.2—4.2 (4H, m), 4.2—4.6 (3H, m), 4.9—5.1 (1H, t, $J = 4$ Hz, O–CH–O).

2-[1-(1,3-Dioxolan-2-yl)-5-hydroxy-3-pentyl]thio-4-methoxyphenol (56)——A mixture of **55** (1.4 g, 3.9 mmol), 2-mercapto-4-methoxyphenol (0.8 g, 5 mmol), K_2CO_3 (0.6 g, 4.4 mmol) and acetone (20 ml) was stirred for 15 h and then filtered, and the filtrate was concentrated *in vacuo*. A 1 N NaOH solution (10 ml) was added to a solution of the above residue in MeOH (30 ml). The resulting mixture was stirred for 5 h, neutralized with 1 N HCl and worked up (AcOEt; H_2O). The residue was purified by column chromatography on silica gel (hexane : AcOEt = 1 : 1) to give **56** (0.7 g, 43%) as a colorless oil. *Anal.* Calcd for $C_{15}H_{22}O_5S$: C, 57.30; H, 7.05. Found: C, 57.51; H, 7.21. IR ν_{max}^{neat} cm⁻¹: 3450—3200 (OH), 1600, 1480, 1275, 1250, 1220, 1205. ¹H-NMR ($CDCl_3$) δ: 1.6—2.2 (6H, m), 2.8—3.2 (1H, m), 3.77 (3H, s, OCH_3), 3.6—4.2 (6H, m), 4.90 (1H, t, $J = 4$ Hz, O–CH–O). MS m/z: 314 (M⁺), 252, 213, 200, 183.

4-[2-(1,3-Dioxolan-2-yl)ethyl]-7-methoxy-3,4-dihydro-2H-1,5-benzoxathiepin (57)——Ph_3P (0.85 g, 3.2 mmol) was added to a solution of **56** (0.9 g, 2.9 mmol) and toluene (10 ml) with stirring. Then, a solution of ethyl azodiformate (0.55 g, 3.2 mmol) in toluene (1 ml) was added dropwise to the above mixture. The whole was stirred for 2 h and concentrated *in vacuo*. The residue was purified by column chromatography on silica gel (hexane : AcOEt = 2 : 1) to give **57** (0.61 g, 71%) as a colorless oil. *Anal.* Calcd for $C_{15}H_{20}O_4S$: C, 60.79; H, 6.80. Found: C, 60.88; H, 6.71. IR ν_{max}^{neat} cm⁻¹: 1595, 1485, 1435, 1280, 1265, 1200. ¹H-NMR ($CDCl_3$) δ: 1.5—2.4 (6H, m), 2.9—3.1 (1H, m, C_4-H), 3.75 (3H, s, OCH_3), 3.7—4.6 (6H, m), 4.88 (1H, t, $J = 4$ Hz, O–CH–O).

7-Methoxy-4-[3-(4-phenyl-1-piperazinyl)propyl]-3,4-dihydro-2H-1,5-benzoxathiepin (58)——A mixture of **57** (680 mg, 2.3 mmol), 50% H_2SO_4 (0.5 ml), H_2O (2 ml) and acetone (10 ml) was stirred for 2 h, then the reaction mixture was worked up (AcOEt; H_2O). N-Phenylpiperazine (0.4 g, 2.5 mmol) was added to a solution of the residual oil in CH_3CN (10 ml) and the mixture was stirred for 4 h. Then, $NaBH_3CN$ (190 mg, 3 mmol) was added. The reaction mixture was stirred for 4 h and then worked up (AcOEt; H_2O). The resulting residue was purified by column chromatography on silica gel (hexane : AcOEt = 1 : 1) to give **58** as a colorless oil, which was converted into the hydrochloride, **58**·2HCl (550 mg, 51%), white crystals, mp 150—153 °C (recrystallized from 50% EtOH). *Anal.* Calcd for $C_{23}H_{30}N_2O_2S$·2HCl: C, 58.59; H, 6.84; N, 5.94. Found: C, 58.48; H, 6.75; N, 5.64. IR ν_{max}^{KBr} cm⁻¹: 3500—3400, 2600—2200, 1595, 1480.

Methyl *cis*-3-Acetoxy-7-methoxy-4-[3-(4-phenyl-1-piperazinyl)propyl]-3,4-dihydro-2H-1,5-benzoxathiepin-4-carboxylate (*cis*-59b)——Acetylation of *cis*-17b with Ac_2O in pyridine gave *cis*-59b as colorless prisms, mp 168—170 °C (recrystallized from AcOEt) in 83% yield. *Anal.* Calcd for $C_{27}H_{34}N_2O_6S$: C, 63.01; H, 6.66; N, 5.44. Found: C, 63.01; H, 6.69; N, 5.40. IR ν_{max}^{KBr} cm⁻¹: 1740 (ester). ¹H-NMR ($CDCl_3$) δ: 2.08 (3H, s, $OCOCH_3$), 3.62 (3H, s), 3.63 (3H, s).

Methyl *cis*-7-Methoxy-3-N-methylcarbamoyloxy-4-[3-(4-phenyl-1-piperazinyl)propyl]-3,4-dihydro-2H-1,5-benzoxathiepin-4-carboxylate (*cis*-60b)——*cis*-60b was prepared by the reaction of *cis*-17b with CH_3NCO in DMF and isolated as the hydrochloride in 89% yield. Recrystallization from EtOH gave *cis*-60b·2HCl as colorless prisms, mp 167—172 °C. *Anal.* Calcd for $C_{27}H_{35}N_3O_6S$·2HCl: C, 53.82; H, 6.19; N, 6.97. Found: C, 53.56; H, 6.42; N, 6.71. IR ν_{max}^{KBr} cm⁻¹: 3400, 1720 (ester). ¹H-NMR (DMSO-d_6-D_2O) δ: 2.75 (3H, s, $NHCH_3$), 3.73 (6H, s, 7-OCH_3 + $COOCH_3$), 5.25 (1H, m, C_3-H).

cis-3-Hydroxy-7-methoxy-4-[3-(4-phenyl-1-piperazinyl)propyl]-3,4-dihydro-2H-1,5-benzoxathiepin-4-carboxylic Acid (*cis*-61b)——A mixture of *cis*-17b (3.0 g, 6.3 mmol), 1 N NaOH (12 ml) and MeOH (40 ml) was stirred at 60 °C for 5 h. After evaporation of the MeOH, the residual mixture was acidified with 1 N HCl. The resulting precipitates were collected by filtration and recrystallized from EtOH to give *cis*-61b (2.4 g, 95%) as colorless crystals, mp 250—260 °C (dec.). *Anal.* Calcd for $C_{24}H_{30}N_2O_5S$·H_2O: C, 60.48; H, 6.77; N, 5.88. Found: C, 60.27; H, 6.73; N, 5.66. IR ν_{max}^{KBr} cm⁻¹: 3600, 3510—3300, 2600—2200, 1640—1590, 1485, 1370, 1210.

Ethyl *cis*-3-Hydroxy-7-methoxy-4-[3-(4-phenyl-1-piperazinyl)propyl]-3,4-dihydro-2H-1,5-benzoxathiepin-4-carboxylate (*cis*-62b)——A mixture of *cis*-61b (1.2 g, 2.5 mmol), Et_2SO_4 (0.5 g, 3.2 mmol), $NaHCO_3$ (1.0 g, 12 mmol) and EtOH (25 ml) was refluxed for 3 h, then worked up (AcOEt; H_2O). The residue was purified by column chromatography on silica gel (hexane : AcOEt = 1 : 1) to give *cis*-62b as colorless oil, which was isolated as the hydrochloride *cis*-62b·2HCl (0.5 g, 42%), colorless prisms, mp 186—188 °C (from EtOH). *Anal.* Calcd for $C_{26}H_{34}N_2O_5S$·2HCl: C, 55.81; H, 6.49; N, 5.01. Found: C, 55.74; H, 6.56; N, 5.03. IR ν_{max}^{KBr} cm⁻¹: 3540 (OH), 1740 (ester). ¹H-NMR (DMSO-d_6-D_2O) δ: 1.30 (3H, t, $J = 7$ Hz, OCH_2CH_3), 3.72 (3H, s, 7-OCH_3), 4.1—4.2 (3H, m, C_2-H + C_3-H), 4.28 (2H, t, $J = 7$ Hz, OCH_2CH_3).

cis-4-Hydroxymethyl-7-methoxy-4-[3-(4-phenyl-1-piperazinyl)propyl]-3,4-dihydro-2*H*-1,5-benzoxathiepin-3-ol (*cis*-63b)——A solution of *cis*-17b (400 mg, 0.8 mmol) in dry Et_2O (10 ml) was added dropwise to a suspension of $LiAlH_4$ (90 mg, 2.4 mmol) and dry Et_2O (20 ml) with stirring. The mixture was refluxed for 0.5 h. Excess $LiAlH_4$ was decomposed by adding H_2O and 15% NaOH. The inorganic deposit was filtered and the filtrate was concentrated *in vacuo*. The residue was recrystallized from AcOEt to give *cis*-62 (300 mg, 80%) as colorless needles, mp 163—165 °C. *Anal.* Calcd for $C_{24}H_{32}N_2O_4S$: C, 64.84; H, 7.25; N, 6.30. Found: C, 64.76; H, 7.31; N, 6.39. IR v_{max}^{KBr} cm^{-1}: 3540 (OH). ^{1}H-NMR (400 MHz) (CDCl$_3$–D$_2$O) δ: 3.923 (1H, dd, J=1.0, 4.9 Hz, C$_3$-H), 3.995 (1H, dd, J=1.0, 12.8 Hz, C$_2$-H), 4.138 (1H, dd, J=4.9, 12.8 Hz, C$_2$-H).

Methyl 8-Methoxy-3-oxo-2,3,4,5-tetrahydro-1-benzoxepin-2-carboxylate (64)——A solution of methyl 3-(4-methoxy-2-methoxycarbonylmethyloxyphenyl)propionate (15 g, 53 mmol) in toluene (200 ml) was added dropwise to a gently boiling suspension of 60% NaH (5.6 g, 140 mmol), *tert*-BuOH (0.4 ml) and toluene (200 ml) (8 h). After refluxing for 0.5 h, the reaction mixture was allowed to stand overnight and then poured into ice-H_2O containing AcOH (10 ml). The organic layer was separated, washed with H_2O, dried and concentrated *in vacuo*. The residue was purified by column chromatography on silica gel (hexane : AcOEt = 4 : 1) to give 64 (9.5 g, 71%) as a colorless oil. *Anal.* Calcd for $C_{13}H_{14}O_5S$: C, 62.39; H, 5.64. Found: C, 62.18; H, 5.86. IR v_{max}^{neat} cm^{-1}: 1760, 1720. ^{1}H-NMR (CDCl$_3$) δ: 2.9—3.1 (4H, m), 3.72 (3H, s), 3.80 (3H, s), 5.00 (1H, s, C$_2$-H), 6.5—7.2 (3H, m).

Methyl 3-Oxo-2,3,4,5-tetrahydro-1-benzothiepin-2-carboxylate (65)——65 was prepared in 81% yield by Dieckmann reaction of methyl 3-(2-methoxycarbonylmethylthiophenyl)propionate, as described for 64. The starting methyl 3-(2-methoxycarbonylmethylthiophenyl)propionate was prepared in 5 steps from methyl 3-(2-hydroxyphenyl)propionate *via* the route involving thiocarbamoylation with dimethylthiocarbamoyl chloride (74% yield), thermal rearrangement at 260—270 °C (70% yield), alkaline hydrolysis, S-alkylation with methyl bromoacetate and esterification with dimethyl sulfate (55% yield). Chromatographic purification of the crude product gave 65 as a colorless oil. *Anal.* Calcd for $C_{12}H_{12}O_3S$: C, 61.00; H, 5.12. Found: C, 61.23; H, 5.28. MS m/z: 236 (M$^+$). IR v_{max}^{neat} cm^{-1}: 1740, (ester), 1700 (CO). ^{1}H-NMR (CDCl$_3$) δ: 2.6—3.4 (4H, m), 3.62 (3H, s, COOCH$_3$), 4.20 (1H, s, C$_2$-H), 6.9—7.7 (4H, m).

Methyl 8-Methoxy-3-oxo-2,3,4,5-tetrahydro-1-benzothiepin-2-carboxylate (66)——66 was similarly prepared by Dieckmann reaction of methyl 3-(4-methoxy-2-methoxycarbonylmethylthiophenyl)propionate in 80% yield. Recrystallization from AcOEt–hexane gave 66 as colorless prisms, mp 76—78 °C. *Anal.* Calcd for $C_{13}H_{14}O_4S$: C, 58.68; H, 5.30. Found: C, 58.59; H, 5.26. IR v_{max}^{KBr} cm^{-1}: 1740 (ester), 1710 (CO). ^{1}H-NMR (CDCl$_3$) δ: 2.9—3.1 (4H, m), 3.68 (3H, s), 3.78 (3H, s), 4.22 (1H, s, C$_2$-H), 6.7—7.4 (3H, m).

Methyl 2-(3-Chloropropyl)-8-methoxy-3-oxo-2,3,4,5-tetrahydro-1-benzoxepin-2-carboxylate (67)——67 was prepared by alkylation of 64 with 3-bromo-1-chloropropane, as described for 2. Chromatographic purification gave a colorless oil. MS m/z: 326, 328 (M$^+$). High-resolution MS Calcd for $C_{16}H_{19}ClO_5$: 326.0919. Found: 326.0925. IR v_{max}^{neat} cm^{-1}: 1750 (ester), 1720 (CO). ^{1}H-NMR (CDCl$_3$) δ: 2.0—2.2 (4H, m), 2.92 (4H, s, C$_4$-H+C$_5$-H), 3.52 (2H, t, J=6 Hz, CH$_2$Cl), 3.64 (3H, s), 3.72 (3H, s), 6.4—7.1 (3H, m). Compound 67 thus obtained was found to contain a small amount of enol ether (2—3%) as a by-product, but was used for the following step without further purification. 68 and 69 were similarly prepared by alkylation of 65 and 66, respectively.

Methyl 2-(3-Chloropropyl)-3-oxo-2,3,4,5-tetrahydro-1-benzoxepin-2-carboxylate (68)——A colorless oil (41% yield). MS m/z: 312, 314 (M$^+$). High-resolution MS Calcd for $C_{15}H_{17}ClO_5S$: 312.0586. Found: 312.0582. IR v_{max}^{neat} cm^{-1}: 1720 (ester, CO). ^{1}H-NMR (CDCl$_3$) δ: 1.7—3.6 (10H, m), 3.65 (3H, s, COOCH$_3$), 7.1—7.8 (4H, m).

Methyl 2-(3-Chloropropyl)-8-methoxy-3-oxo-2,3,4,5-tetrahydro-1-benzothiepin-2-carboxylate (69)——A colorless oil (50% yield). MS m/z: 342, 344 (M$^+$). High-resolution MS Calcd for $C_{16}H_{19}ClO_4S$: 342.0692. Found: 342.0693. IR v_{max}^{neat} cm^{-1}: 1740 (ester), 1700 (CO). ^{1}H-NMR (CDCl$_3$) δ: 1.8—2.0 (4H, m), 2.8—3.0 (4H, m), 3.42 (2H, t, J=7 Hz, CH$_2$Cl), 3.62 (3H, s), 3.72 (3H, s), 6.7—7.4 (3H, m).

Methyl *cis*- and *trans*-2-(3-Chloropropyl)-3-hydroxy-8-methoxy-2,3,4,5-tetrahydro-1-benzoxepin-2-carboxylate (*cis*- and *trans*-70)——NaBH$_4$ reduction of 67 in an ice-cooled solution of THF and MeOH (1:4) and subsequent column chromatography on silica gel (hexane : AcOEt = 3 : 1) gave *cis*-70 (from the first fraction) and *trans*-70 (from the second fraction).

cis-70: A colorless oil (46% yield). *Anal.* Calcd for $C_{16}H_{21}ClO_5$: C, 58.45; H, 6.44. Found: C, 58.66; H, 6.59. IR v_{max}^{neat} cm^{-1}: 3500 (OH), 1740 (ester). ^{1}H-NMR (CDCl$_3$) δ: 1.8—2.0 (4H, m), 2.4—3.5 (6H, m), 3.72 (3H, s), 3.75 (3H, s), 6.5—7.2 (3H, m).

trans-70: A colorless oil (44% yield). *Anal.* Calcd for $C_{16}H_{21}ClO_5$: C, 58.45; H, 6.44. Found: C, 58.78; H, 6.21. IR v_{max}^{neat} cm^{-1}: 3500 (OH), 1740 (ester). ^{1}H-NMR (CDCl$_3$) δ: 1.9—2.0 (4H, m), 2.4—3.2 (4H, m), 3.48 (2H, t, J=7 Hz, CH$_2$Cl), 3.66 (3H, s), 3.72 (3H, s), 4.0—4.2 (1H, m), 6.46—7.02 (3H, m).

Methyl *cis*-2-(3-Chloropropyl)-3-hydroxy-2,3,4,5-tetrahydro-1-benzothiepin-2-carboxylate (*cis*-71)——NaBH$_4$ reduction of 68 gave *cis*-71 (80% yield) as colorless prisms, mp 108—110 °C (recrystallized from AcOEt). *Anal.* Calcd for $C_{15}H_{19}ClO_3S$: C, 57.23; H, 6.08. Found: C, 57.27; H, 6.11. IR v_{max}^{KBr} cm^{-1}: 3500 (OH), 1730 (ester). ^{1}H-NMR (400 MHz) (DMSO-d_6–D$_2$O) δ: 4.051 (1H, dd, J=2.7, 5.4 Hz, C$_3$-H).

Methyl *cis*-2-(3-Chloropropyl)-3-hydroxy-8-methoxy-2,3,4,5-tetrahydro-1-benzothiepin-2-carboxylate (*cis*-72)——NaBH$_4$ reduction of 69 gave *cis*-72 (74% yield) as a colorless oil. *Anal.* Calcd for $C_{16}H_{21}ClO_4S$: C, 55.73; H, 6.14.

Found: C, 55.98; H, 6.00. IR ν_{max}^{neat} cm^{-1}: 3530 (OH), 1740. ^{1}H-NMR (400 MHz) (DMSO-d_6-D$_2$O) δ: 4.056 (1H, dd, $J=2.7$, 5.4 Hz, C$_3$-H).

Methyl *cis*-3-Hydroxy-8-methoxy-2-[3-(4-phenyl-1-piperazinyl)propyl]-2,3,4,5-tetrahydro-1-benzoxepin-2-carboxylate (*cis*-73, Table II)——A mixture of *cis*-70 (1.0 g, 3.1 mmol), *N*-phenylpiperazine (1.1 g, 6.8 mmol), and KI (0.25 g, 1.5 mmol) was stirred at 90 °C for 3 h. The reaction mixture was subjected to column chromatography on silica gel (hexane: AcOEt : MeOH = 30 : 20 : 1) to give *cis*-73 (0.65 g, 47%) as colorless prisms (recrystallized from AcOEt). IR ν_{max}^{KBr} cm^{-1}: 3400 (OH), 1760, 1730. ^{1}H-NMR (400 MHz) of *cis*-73·2HCl (DMSO-d_6-D$_2$O) δ: 4.064 (1H, dd, $J=3.4$, 3.9 Hz, C$_3$-H).

Similar treatment of *trans*-70, *cis*-71 and *cis*-72 gave *trans*-73, *cis*-74 and *cis*-75, respectively (Table II).

Methyl *trans*-3-Hydroxy-8-methoxy-2-[3-(4-phenyl-1-piperazinyl)propyl]-2,3,4,5-tetrahydro-1-benzoxepin-2-carboxylate (*trans*-73)——Recrystallization of the hydrochloride from MeOH–Et$_2$O gave *trans*-73·2HCl as colorless crystals. ^{1}H-NMR (400 MHz) (DMSO-d_6-D$_2$O) δ: 4.070 (1H, dd, $J=2.7$, 7.3 Hz, C$_3$-H).

Methyl *cis*-3-Hydroxy-2-[3-(4-phenyl-1-piperazinyl)propyl]-2,3,4,5-tetrahydro-1-benzothiepin-2-carboxylate (*cis*-74)——Recrystallization from AcOEt gave *cis*-74 as colorless prisms. IR ν_{max}^{KBr} cm^{-1}: 3450—3100 (OH), 1720 (ester).

Methyl *cis*-3-Hydroxy-8-methoxy-2-[3-(4-phenyl-1-piperazinyl)propyl]-2,3,4,5-tetrahydro-1-benzothiepin-2-carboxylate (*cis*-75)——Recrystallization of the hydrochloride from 30% EtOH gave *cis*-75·HCl as colorless crystals. ^{1}H-NMR (400 MHz) (DMSO-d_6-D$_2$O) δ: 4.056 (1H, dd, $J=2.2$, 5.1 Hz, C$_3$-H).

X-Ray Analyses of *cis*-17b, *cis*-50b, *cis*-58b, *cis*-71 and *cis*-73——All single-crystal measurements were made with a Rigaku AFC-5 automatic diffractometer. The structures were solved by the direct method[27] and refined by a block-diagonal least-squares method[28] using unit weight. In the final refinement, non-hydrogen and hydrogen atoms were refined with anisotropic and isotropic temperature factors, respectively. Details of the X-ray analyses will be published elsewhere.

Serotonin S$_2$-Receptor-Blocking Activity and Adrenergic α_1-Receptor-Blocking Activity *in Vitro*——Pig hearts were obtained from a slaughterhouse under ice-cooling and the left circumflex or anterior descending coronary artery was dissected out within 3 h after death. The coronary artery was cut into a ring preparation of 3 mm in width. On the other hand, the thoracic aorta was dissected out from albino rabbits (2—3 kg body weight, male) after exsanguination. The rabbit aorta was cut into a spiral preparation of about 2 mm in width and about 2 cm in length. These blood vessel preparations were suspended in organ baths containing 20 ml of Krebs–Henseleit solution with a pair of suspending hooks. One of the hooks was fixed to the bottom of the organ bath, while the other was connected to a strain-gauge transducer, and the tension developed by these preparations was isometrically measured. The organ bath was maintained at 37°C, and the Krebs–Henseleit solution was saturated with a gas mixture of 97% O$_2$ + 3% CO$_2$. As agonists, serotonin (10^{-6} M) and norepinephrine (10^{-7} M) were used in the porcine coronary and rabbit aortic preparations, respectively.

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